HUMAN PSYCHOPHARMACOLOGY, VOL. 4, 169–190 (1989)

EEG-Brain Mapping, Psychometric and Psychophysiological Studies on Central Effects of Kavain – A Kava Plant Derivative

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In a double-blind, placebo-controlled study the encephalotropic and psychotropic effects of kavain-a synthetic kava plant derivative as compared with clobazam were investigated, utilizing EEG brain mapping, psychometric and psychopysiological analyses. 15 normal volunteers received randomized in weekly intervals single oral doses of placebo, 200 mg, 400 mg and 600 mg kavain as well as 30 mg clobazam as reference compound. EEG recordings, psychometric tests, evaluations of pulse, blood pressure and side effects were carried out at the hours 0, 1, 2, 4, 6 and 8. Brain maps of drug induced pharmaco-EEG changes (pharmaco-EEG maps) demonstrated that kavain exerted a significant action on the human brain function as compared with placebo characterized by a dose-dependent increase of delta, theta and alpha 1 activity while alpha 2, beta activity and the centroid of the total activity decreased. These findings are indicative of a sedative effect which was, however, in type quite different from that of the 1·5 benzodiazepine. The latter produced a decrease of delta, theta, alpha 1 and alpha 2 and an increase of beta activity while the total centroid was accelerated. Interestingly, 200 mg kavain induced with a decrease of delta and beta activity and an increase of alpha activity and of total power also vigilance promoting effects. Psychometric investigations demonstrated also clear differences between the two compounds at the behavioural level. Kavain improved the noopsyche as compared with placebo in all 3 doses as there was a significant improvement in intellectual performance (Pauli test), attention, concentration, reaction time and motor speed (rigidity test), while opposite findings were observed after 30 mg clobazam. In regard to thymopsychic variables such as drive, wakefulness, affectivity, mood, well-being, 200 mg kavain produced an improvement as compared with placebo while 600 mg kavain produced sedation as did 30 mg clobazam. Psychophysiological evaluations resulted in only minimal findings. Time efficacy calculations demonstrated after kavain a pharmacodynamic peak in the 1st to the 2nd hour then a drop and a second peak in the 8th hour while clobazam produced maximal central effects in the 1st hour which declined thereafter to show a second peak in the 6th hour. Topographically, most encephalotropic effects were found after kavain in the frontal, after clobazam in the central and parietal areas. Evaluations of pulse, blood pressure and side effect demonstrated good tolerability of both compounds with 30 mg clobazam producing more sedation than kavain.

KEY WORDS—Human psychopharmacology, EEG brain mapping, psychometry, psychopysiology, noopsyche, thymopsyche, kavain, kava plant, clobazam, benzodiazepine

INTRODUCTION

Although for centuries an extract of the kava plant (piper methysticum) has been utilized by the inhabitants of the South Pacific for both its anti-anxiety and psycho-stimulatory effects, and despite the fact that its pharmacological active substances (kavain, dihydrokavain, methysticin, dihydromethysticin and yangonin) have been synthesized in the late 50s, with the main kava-pyrone, e.g. kavain being marketed since the early 70s, there is a paucity of well-controlled clinical pharmacological studies. Animal pharmacological data showed with increasing doses central sedation starting with motor hypo-activity and muscle relaxation while respiration was unchanged. It was quite intriguing that attention was unhampered until lethal doses. The muscle relaxant effect was reminiscent of the action of mephenesin, meprobamate and the benzodiazepines. Kavain and the other kava pyrones exerted, however, stronger anti-convulsant effects than mephenesin and differed in that regard only marginally from the most typical anti-convulsants phenytoin and phenobarbital. Moreover, there was

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0885-6222/89/030169-22$11.00

Accepted 24 May 1989

also a marked spasmolytic effect. Early human pharmacological investigations in 90 healthy young volunteers demonstrated that kavain in doses of 200 mg–1·0 g induced emotional and muscular relaxation, affective stabilization as well as a trend towards improvement of mental performance (Kretschmer, 1970). The latter could be confirmed by a double-blind, placebo-controlled trial involving 100 mg Kavain b.i.d. given over 4 weeks with the verum-treated subjects showing relaxation, improvement of mood, less sensibility towards outside stimuli as well stabilization of drive (Kretschmer, 1974). In higher doses subjects exhibited either diurnal tiredness or signs of activation. Kryspin-Exner (1974) investigated 50 chronic alcoholics in a double-blind, placebo-controlled trial involving 3 × 200 mg kavain and noted superiority of the drug over placebo in regard to withdrawal symptoms. Studying the effects of 2 × 200 mg kavain on motor reaction time as well as visual-mental performance, Krueger and Kell (1977) found a lengthening of the former while at the same time an improvement of the latter after one week treatment. In a double-blind, placebo-controlled trial Ambrozi (1979) noted in 60 healthy volunteers around the age of 50 an unchanged critical flicker frequency, an improvement in the digit span test as well as an improvement of complex reaction time. Finally Krach (1986) described in 41 patients with psychovegetative disturbances an improvement in initial insomnia, drive and gastrointestinal complaints after two weeks of treatment as compared with placebo.

The aim of the present double-blind, placebo-controlled human pharmacological trial was to investigate the encephalotropic and psychotropic properties of kavain[1] in normal healthy volunteers utilizing pharmaco-EEG brain mapping, psychometric and psychophysiological techniques.

METHODS

15 healthy normal volunteers (8 males, 7 females), aged 22–43 years (mean 27), weighing from 50–84 kg (mean 64 kg) and ranging in height from 158–199 cm (mean 174 cm) participated in the double-blind, placebo controlled cross-over study. They were not allowed to take any psychoactive drugs three weeks before and/or during the study. Subjects received at weekly intervals in random order following single oral doses: placebo, 200 mg, 400 mg and 600 mg *d, l*-kavain, as well as 30 mg clobazam. The study was performed in accordance with the rules and regulations for the conduct of clinical trials stated in the Declaration of Helsinki, as revised by the World Medical Assembly at Tokyo and Venice. An informed written consent was obtained from all subjects. The volunteers were free to withdraw from the study at any point in time. Blood sampling, EEG recordings and evaluations of blood pressure, pulse and side effects were carried out before as well as 1, 2, 4, 6 and 8 hours post drug. Psychometric tests were carried out at the same times.

Neurophysiological investigations included a 3 min. vigilance-controlled EEG (V-EEG), a 4 min. resting EEG (R-EEG) and a 4 min. orienting response recording (which will be reported elsewhere) by means of a 17-channel Nihon Kohden 4317 F polygraph (time constant: 0·3 sec; high frequency response: 35 Hz; frequency range: 0·5–35 Hz; amplification: approximately 1: 20,000; maximal noise level: 2 μV peak-to-peak) with the subjects lying relaxed with eyes closed in an electrically-shielded room. Electrodes were attached according to the international 10/20 system to the scalp. During the V-EEG recordings, the technician tried to keep the subjects alert; as soon as drowsiness patterns appeared in the record, the subjects were aroused. 17 leads (F_p1, F_p2, F7, F3, F4, F8, T3, C3, Cz, C4, T4, T5, P3, P4, T6, 01 and 02 to averaged mastoids) were digitized on-line by a Hewlett-Packard Vectra system with a sampling frequency of 102·4 Hz, resulting in a frequency resolution of 0·2 Hz (Anderer *et al.*, 1987; Saletu *et al.*, 1987). Spectral analysis was performed using the fast Fourier transform technique in floating-point arithmetic to maintain precision.

Generally, a single spectral distribution curve from one electrode and for a particular clinical state (e.g., pretreatment, treatment) and various recording procedures (e.g. V-EEG, R-EEG) is formed as the mean of 5-sec spectra from artifact-free EEG during that state. Artifact-free epochs were selected using the Automatic Artifact Rejection Method (AARM) as described by Anderer *et al.* (1987). The mean spectral curves contained data from 1·3 – 35 Hz quantified into 36 variables: total power (TP); the absolute and relative power in 12 different frequency bands; the dominant frequency (DF) (in Hz), the relative (RP) and absolute (AP) power of the dominant frequency; further, the center-of-

[1]Kavain (Neuronika^R, Mosaro^R) was kindly supplied by Klinge Pharma, Münich, FRG.

gravity frequencies (centroids) (C) and their standard deviations (S) of the combined delta and theta (DT), alpha (A) and beta (B) bands as well as of the total activity (TP). 17 numbers representing variables from each of the 17 electrodes are mapped onto a 64 × 64 numerical matrix. Each interpolated value is based on the cubic distance from the values at the three nearest electrodes. The resulting matrix is maintained for statistical analysis and displayed as a video image in pseudocolor scaled format. In this manner topographic images can be viewed that represent the values and spatial distribution of 36 variables and are subsequently printed by the Hewlett Packar 'paint jet'.

To display the differences in the distribution of particular EEG variables before and after drug administration, the significance probability mapping (Bartels and Subach, 1976; Duffy *et al.*, 1981; Saletu *et al.*, 1987) was used. Mean and variance matrices of the Q-EEG variables of 15 subjects before administration were compared with the similar matrices 1, 2, 4, 6 and 8 hours postdrug. Results of this exploratory process were expressed in t-scores and displayed as SPM images. With such displays, regions of drug-induced changes are grapically delineated for each variable separately. Subsequently, the same method was utilized to demonstrate differences between drug-induced and placebo-induced alterations ('pharmaco-EEG maps').

Psychometric and psychophysiological tests

Noopsychic tests included the alphabetical cross-out test (AD-test = Alphabetischer Durchstreich-test) of Grünberger (1977) for evaluation of the quantitative aspects (total score), qualitative aspects (errors in percent of the total score) of attention and the attention variability (difference between extreme scores); the Pauli test (correct calculations; errors); numerical memory (short-term memory) (Grünberger, 1977); the psychomotor activity (Feinmotoriktest) of Grünberger (1977); the reaction time (in msec) as determined on the Viennese reaction-apparatus and the errors occurring in the test, and a microprocessor-assisted rigidity and perseveration test (Grünberger *et al.*, 1988).

Thymopsychic assessments consisted of the von Zerssen Bf-S scale (von Zerssen *et al.*, 1970) for evaluation of subjective well-being; a semantic differential polarity profile for changes in affectivity including the dimensions wakefulness, concentration, mood and extraversion (Osgood *et al.*, 1975); and four 100 mm visual analogue scales for self-rating of mood, wakefulness, affectivity and drive.

Psychophysiological measures included the critical flicker frequency (CFF, descending threshold); and microprocessor-assisted measurements of the static and dynamic pupillometry and skin conductance (SCL, in μmhos) (Grünberger *et al.*, 1984).

Exploratory statistical analyses included discriminant analysis, MANOVA, ANOVA, and Newman-Keuls test, the Duncan test, the t-test, as well as the Friedman and multiple Wilcoxon test.

RESULTS

Neurophysiological Findings

1. Pharmaco-EEG maps – multivariate analysis

In order to obtain an answer to the question whether or not the investigational drugs exert significant effects on the human brain as compared with placebo and at which times, MANOVAs were performed (for each of the 17 electrodes) considering group (drug, placebo), time (pre, post) and relative power values in all 9 Q-EEG frequency bands. The latter were transformed (ln (power % / (100-power %)) to fulfil the conditions for the MANOVA (homogeneity of the variances and co-variances as well as the symmetric unimodal distribution (Gasser *et al.*, 1982). Hotelling's T^2-values were used to avoid Type I errors with inflated df and were imaged in terms of brain maps (Plate 1).

As can be seen, 200 mg kavain produced only subtle changes in the 2nd and 8th hour in various locations, while 400 and 600 mg produced slightly more changes between the 1st hour and 8th hour with a maximum in the initial hours. In contrast, 30 mg clobazam produced consistent CNS changes over the vertex, central, and parietal regions with two peaks in the 1st and 6th hour.

2. Pharmaco-EEG maps – univariate analysis

In order to demonstrate central effects after the 4 compounds in each of the 28 EEG variables in detail, topographic brain maps of drug-induced changes as compared with placebo-induced alterations are described in the following chapter, which are based on V-EEG recordings obtained 1 hour after drug intake. As was shown by multivariate analysis and will be discussed later, this was

generally the time of the pharmacodynamic peak effect (see also psychometric data).

200 mg kavain produced, as compared with placebo, no significant changes in absolute power of the delta, theta, alpha 1, alpha 2 and beta bands, with the exceptions of an increase of beta power right occipitally (O) and a decrease of delta power right centrally (C) and left fronto-temporally (FT) in the 1st hour (Plate 2). Regarding changes in the individual beta bands, there was a slight augmentation of beta 2 power in the right occipital (O) and frontotemporal (FT) regions in the 1st and 2nd hour, respectively. On the other hand, an attenuation of beta 3 power occurred in the 4th hour over both frontal (F) areas, while beta 4 power was augmented right FT in the 8th hour.

In regards to relative power, 200 mg kavain produced as compared with placebo, a decrease of delta activity in the left FT and right C area in the 1st hour (Plate 3), while in the 4th to the 8th hour an increase in the left F but also over the left temporal (T) and occipital-temporal (OT) area occurred. Theta was augmented only in the 2nd hour over the left C area. Alpha 1 activity increased in the 1st hour left FT and right C (Plate 3), and decreased in the 8th hour over the right OT and T regions. Alpha 2 activity showed only a decrease in the 4th hour over the left T area. Beta 1 activity increased over the vertex in the 6th hour, beta 2 activity decreased in the 4th and 8th hour left F. Beta 3 showed only a decrease in the 1st and 2nd hour left C, while beta 4 increased over the right O. Beta 5 showed an increase in the 6th and 8th hour over the right C, left F and T areas. Combined beta were reduced in the 1st hour left C (Plate 3) and bifrontally in the 4th hour. The dominant frequency showed only an acceleration in the 8th hour over the left FT and C area but no changes in regard to absolute and relative power.

Total power increased occipitally in the 1st hour (Plate 4). The centroid of the total activity slowed down in the 2nd hour over both P and the left OT area, in the 4th and 8th hour over the left F region. The deviation of the centroid of the total activity increased in the 6th and 8th hour over the left T and F areas. A detailed analysis of the centroid of the combined delta/theta activities exhibited a slowing in the 6th and 8th hour over the left T temporal (T), OT and O areas. The centroid deviation of the combined delta/theta activities increase in the 1st hour left FT but decreased in the 2nd, 6th and 8th hour left T and in the 8th hour only right OT. The centroid of the alpha activity increased right C in the 1st hour (Plate 4) and in the right OT in the 6th hour while the centroid deviation did not exhibit any significant findings. The centroid of the combined beta activity decreased in the 2nd hour over the right T and increased over the right FT in the 6th hour. The centroid deviation increased from the 1st–8th hour in different areas (F, right C and OT and T).

400mg kavain produced, as compared with placebo, a decrease of delta power in the 1st and 6th hour over the right C (Plate 2) and increase over the left C in the 2nd and 4th hour. Theta power increased over the right FT area in the 2nd, 4th and 8th hour. No significant changes occurred in alpha 1 power while alpha 2 power decreased in the 1st and 4th hour mostly over the left P and right C areas. Beta 1 activity decreased in the 8th hour over the vertex and right C area, beta 3 in the 1st and 2nd hour over the left C and T as well as vertex regions. Over the vertex region there was an attenuation of beta 4 power in the 1st, 2nd and 4th hour. Thus, total beta power declined over the vertex and left C area in the 1st, 6th and 8th hour.

In regard to relative power, we observed an augmentation in the delta range over the left C and T area in the 2nd hour as well as over the right T in the 8th hour. There were no significant changes in the theta and alpha 1 activity while alpha 2 activity was attenuated in the 1st, 2nd and 4th hour over the left T and initially only over the left C and vertex regions (Plate 3). Beta 1 activity decreased over the left F and right FT area in the 1st hour as well as over the vertex in the 8th hour. Beta 2 activity decreased over the left T in the 1st hour and over the left F region in the 6th hour as well as bifrontally in the 8th hour. Beta 3 decreased over the left C in the 1st and 2nd hour and over the left F region in the 8th hour. Similarly, we saw a decrease of beta 4 activity over the vertex in the 1st, 2nd and 8th hour, as was the case for relative power of the total beta activity (Plate 3).

The dominant frequency was accelerated occipitally in the 1st hour and parietally in the 6th and 8th hour. There were no changes in regard to absolute and relative power of the dominant frequency. Total power was augmented in the 2nd hour left frontally, the centroid of the total activity was slowed down in the 1st and 2nd hour over the left C and right FP area (Plate 4) while over both frontal regions in the 8th hour. The centroid deviations decreased over the vertex in the 1st and 8th hour. In detail, we observed in regard to the centroid of the combined delta/theta activities a slowing over both T and the left OT areas in the 8th

hour, with its centroid deviation increasing over the F areas in the 1st and 2nd hour while declining in the 2nd and 8th hour left T. The centroid of the combined alpha activity decreased in the 2nd hour over the left T ara with its deviation increasing in the 6th hour over the left O and the right FT. The centroid of the combined beta activity decreased in the 2nd and 6th hour over the right T region, in the 2nd hour over the vertex and in the 8th hour over the left C areas. The centroid deviation of the beta activity decreased in the 2nd-6th hour over the left FT while it increased over the right T area.

600 mg kavain produced, as compared with placebo, in regard to delta power an increase in the 1st hour over the right OT, F and left OT regions (Plate 2), in the 2nd hour bioccipitally as well as over the right C and both F areas, in the 4th hour biocipitally, left OT and left F. Theta power increased also over both O and Fp areas from the 1st and 4th hour with an additional augmentation over the left C and F areas in the 2nd and in the left T and right C in the 4th hour. In the 8th hour theta was augmented over both FT and the right OT regions. There were no significant changes in absolute power of the alpha 1, alpha 2 and beta 1 bands. Beta 2 power decreased over the right F and both Fp areas in the 6th to the 8th hour. Beta 3 activity declined in the 2nd and 6th hour left C and right O. Beta 4 power declined in the 6th hour over the left OT and Fp. Finally, beta 5 power increased over the right O region in the 1st hour and in the left T area in the 4th hour while it decreased in the 6th and 8th hour over the Fp and right F regions. Thus, total beta power increased re O in the 1st hour (Plate 2), but declined in the 2nd, 6th and 8th hour over both F and right F areas.

Relative power of the delta activity increased in the 2nd hour over the right O, in the 6th hour over the left C area. Theta activity increased in the 2nd hour over the right OT and FT and left C regions with the former being also significant in the 4th hour and the latter in the 6th hour while in the 8th hour there was a marked and extended augmentation over the whole scalp except the vertex, both T, left FT and F and O regions. Alpha 1 activity remained unchanged while alpha 2 activity was markedly attenuated in the 1st hour in both OT, the right O as well as left P, T, C and vertex regions (Plate 3). In the 2nd hour there was an attentuation over the left T and right O, in the 4th hour over the left T and right O, in the 4th hour over the left parietal region. Beta 1 activity showed only an augmentation over the left FT and right T regions, beta 2 activity an attentuation over the left F area in the 6th hour. Beta 3 activity declined over the left C area in the 2nd, 4th and 8th hour. Beta 4 activity showed a decline over the right F area in the 8th hour which was also the case with beta 5 activity. Relative power of total beta decreased only in the 8th hour over the right F region.

The dominant frequency slowed down in the 2nd hour over the left OT region but was accelerated in the 6th and 8th hour over the left P and FT area, respectively. There were no significant changes in absolute and relative power of the dominant frequency. Total power was augmented O in the 1st and 2nd hour (Plate 4). The centroid of the total activity slowed down in the 2nd hour over the left P, C and F regions, which was also seen in the 8th hour and only in the left F and right Fp regions in the 6th hour. The centroid deviations declined over both Fp areas in the 1st throughout the 6th hour with an addition decrease in the 8th hour over the right F area. In detail, the centroid of the combined delta/theta activity showed no significant findings, its centroid deviation a decrease over the P region in the 1st hour and an increase over the right T region and a decrease over the right OT area in the 8th hour. The alpha centroid declined in the 2nd hour over the left C and O areas, while in the 8th hour there was no acceleration over the left FT and O region. The centroid deviation of the alpha activity increased over the right P from the 2nd throughout the 6th hour. In addition there was a decline in the 8th hour over the vertex. The beta centroid decreased significantly and markedly over the vertex, both Fp, right C and P area in the 2nd hour, with the Fp attenuation seen also in the 4th, 6th and 8th hour. In the 6th hour there was, however, an augmentation over the left T area as well as attentuation over the right FT region. The deviation of the beta centroid increased over the right P region in the 2nd hour, over the vertex and frontal areas in the 4th hour and 6th hour.

30 mg clobazam produced, as compared with placebo, a delta power decline over both FT areas in the 1st throughout the 4th hour with an additional attentuation over the right T and C area in the 1st hour (Plate 2), left P region in the 4th hour while in the 6th hour only over the right T area the attentuation was observed. Theta power declined markedly and extensively in the 1st, 6th and the 8th hour almost over all the whole brain (Plate 2) while in the 2nd hour mostly over the anterior portion of the brain. Alpha 1 power showed an attentuation in the 1st, 6th and 8th hour

over the rigth T region and in the 6th hour also over the left T and C areas. Alpha 2 power declined also over the left Fp, F, C, and P as well as right Fp regions in the 1st hour (Plate 2) while in the 4th and 6th hour only an attentuation over the left P, left and right T and right C area was observed, respectively. Beta 1 power was augmented over the vertex and central region in the 1st throughout the 4th hour, beta 2 activity from the 1st throughout the 8th hour again over the vertex and the C regions with an additional augmentation over both P areas in the 1st and 2nd hour and right O in the 1st hour. In the 2nd and 4th hour, we observed also an augmentation right FT. Beta 3 power was augmented in the 1st throughout the 6th hour over the vertex and P regions. Beta 4 power showed an augmentation in the same areas up to the 8th hour. Beta 5 power was only augmented in the 1st hour over the right C and the 6th over the left C region. Total beta power increased from the 1st – 8th hour over the vertex both C and P regions (Plate 2).

Relative power of the delta activity increased over the left F region in the 4th throughout the 8th hour with an additional augmentation in the 6th hour over the left O and in the 8th hour over the right T region. In contrast, theta activity declined extensively in the 1st hour almost over the total anterior brain (Plate 3), which persisted until the 6th hour in the left FT and vertex region. In the 8th hour still an attentuation was observed over the left FT and T regions. Alpha 1 activity did not change significantly with the exception of an attenuation over the left OT area while alpha 2 activity decreased in the 1st hour over the left C, T and right O and in the 2nd hour over the left T area as was the case in the 6th hour. Beta 1 activity was augmented over both central regions from the 1st throughout the 6th hour with additional increases in the 1st hour over left F, FT and right T areas. Similar findings were observed in the 2nd and 4th hour while in the 6th hour the greatest extension of beta augmentation was observed (with only the F, Fp, T and left O regions being spared). On the other hand, in the 8th hour only the left C area exhibited still an augmentation of beta 1 activity. Beta 2 activity was augmented in the 1st hour all over the brain except both T regions, which decreased in extent in the 2nd and 4th hour but reached the same locations in the 6th hour. In the 8th hour beta 2 activity still increased as compared with placebo over both FT, C, P and the left O and F regions. Beta 3 and beta 4 activities showed an augmentation mostly over both FT, C and P areas with two peaks in the 1st and 6th hour. Finally, beta 5 activity increased only locally over the vertex and central regions between the 1st and 6th hour with the greatest expansion reached in the 6th hour (as the P regions were reached as well). The augmentation of relative power in the total beta range in the 1st hour is depicted in Plate 3, with its widest expansion in the 6th hour.

The dominant frequency declined in the 2nd hour over the right FT and FP and in the 4th hour over the right O region. The absolute power of the dominant frequency declined also over the right T area in the 1st and 2nd hour and over the left FT and T, as well as right F region in the 6th hour. Relative power of the dominant frequency declined only in the 1st hour over the right T and in the 6th hour over the right C area. Total power was attenuated in both FT regions in the 1st throughout the 8th hour (Plate 4), with an additional attenuation in the 6th hour over both F, C, O and the vertex region.

The centroid of the total activity showed an acceleration over large parts of the brain including the FT, F, C and P areas, which was most pronounced in the 1st hour to decline in extension in the 2nd, 4th and 6th hour and to disappear in the 8th hour (Plate 4). The centroid deviation of the total power spectrum showed also an increase at the very same location which differed only in time in as much as the greatest expansion was noted in the 6th hour, with a still visible significant increase in the 8th hour over both C and P areas. In detail, the centroid of the combined delta/theta activities slowed down mostly in the 1st hour over the left F, T, the vertex and both OT and P areas (Plate 4). In the 2nd hour, a significant decrease was noted only over the left T and right F area, in the 4th hour only over the left T region. In the 6th hour the area showing a slowing of the centroid increased again to involve the left F, T, OT, O and right OT regions and extending in the 8th hour to the right T, left C and vertex field. The centroid deviation of the combined delta/theta declined as well in the 1st and 4th hour over the right T and in the 6th hour over both OT and the right FT and in the 8th hour over the left P, O and right OT areas. The alpha centroid showed only one significant change in the 1st hour in terms of a O decline (Plate 4). The centroid deviation of the alpha activity increased only in the 1st hour over the right C region. The centroid of the combined beta activities decreased in the 1st hour over both Fp areas (Plate 4) which was seen in the 2nd and 6th hour only over the left side. The centroid

Table 1. Time-efficacy relations after single oral doses of 200, 400, and 600 mg Kavain and 30 mg Clobazam in 15 healthy subjects based on sign-adjusted differences to placebo in 28 V+R EEG variables (rank sums, mean of 17 leads)

Treatment	0 Hr	1 Hr	2 Hr	4 Hr	6 Hr	8 Hr	χ^2_r	Multiple Wilcoxon
B 200 mg Kavain	86,6	105,4	106,5	114,6	77,9	97,2	9,9+	
C 400 mg Kavain	71,2	118,6	105,6	93,1	88,9	110,5	15,0*	0:1*, 0:8$^+$
D 600 mg Kavain	79,5	102,9	117,2	91,4	94,4	102,7	8,6	0:2$^+$
E 30 mg Clobazam	63,1	123,6	94,1	98,6	117,2	91,4	23,6**	0:1, 6**

$^+p < 0,10$
$^*p < 0,05$
$^{**}p < 0,01$

deviation of the combined beta activities increased over the right P in the 2nd and 4th hour and declined over the right Fp areas in the 2nd and 4th hour as well as over the left T region in the 8th hour.

3. Cerebral bioavailability determined by multi-lead EEG analysis

Time efficacy relations were calculated utilizing the Friedman's and multiple Wilcoxon test of placebo-corrected changes in 28 V- and R-EEG variables obtained in 17 derivations (Table 1).

As can be seen, kavain produced CNS changes showing the first peak in the 1st to the 2nd hour and a second peak in the 8th hour, while 30 mg clobazam showed a clear peak effect in the 1st hour, a decrease thereafter and a second peak in the 6th hour (Table 1). The locations of greatest changes over time lay generally after kavain over the anterior brain regions, while after 30 mg clobazam over the right parietal area (Plate 5).

If one calculates *does-efficacy relations* of kavain based on the same method (Friedman - and subsequent Wilcoxon test of sign - adjusted changes in 28 EEG variables obtained from 17 leads), 400 and 600 mg kavain could be significantly differentiated from placebo but also the 200 mg from the 400 mg dosage (Table 2). Again, the areas of greatest inter-drug differences lay in the frontal part of the brain, with a right-sided accentuation (Plate 5).

Psychometric and psychophysiological findings

1. Noopsychic changes - multivariate analysis

A multivariate statistical analysis by means of MANOVA and discriminant analysis considering changes in 9 noopsychic variables at all times (0, 1, 2, 4, 6 and 8th hour) after all 5 substance demonstrated, that after placebo a slight deterioration occurred in noopsychic performance which was statistically significant as compared with pre-treatment in the 2nd hour (Figure 1). In contrast, kavain produced in the 200 and 400 mg dosage only minimal alterations and in the 600 mg dosage a trend towards improvement of noopsychic

Table 2. Dose/treatment-efficacy relations after single oral doses of placebo, 200, 400 and 600 mg Kavain in 15 healthy subjects based on sign-adjusted changes in 28 V+R-EEG variables (rank sums, means of 17 leads)

Time	A Placebo	B Kavain 200 mg	C Kavain 400 mg	D Kavain 600 mg	χ^2_r	Multiple Wilcoxon
1 Hr	54,6	69,0	84,2	72,1	9,4*	A:C*
2 Hr	52,5	66,7	77,2	83,6	12,1**	A:C$^+$, A:D **
4 Hr	60,1	76,7	71,4	71,8	3,2	n.s.
6 Hr	64,4	62,5	78,6	74,5	4,0	n.s.
8 Hr	54,9	65,8	84,1	74,3	10,3*	A:C*
Total	286,6	340,7	396,4	376,3	30,3**	A:B+, A:C, D** B:C*

$^+p < 0,10$
$^*p < 0,05$
$^{**}p < 0,01$

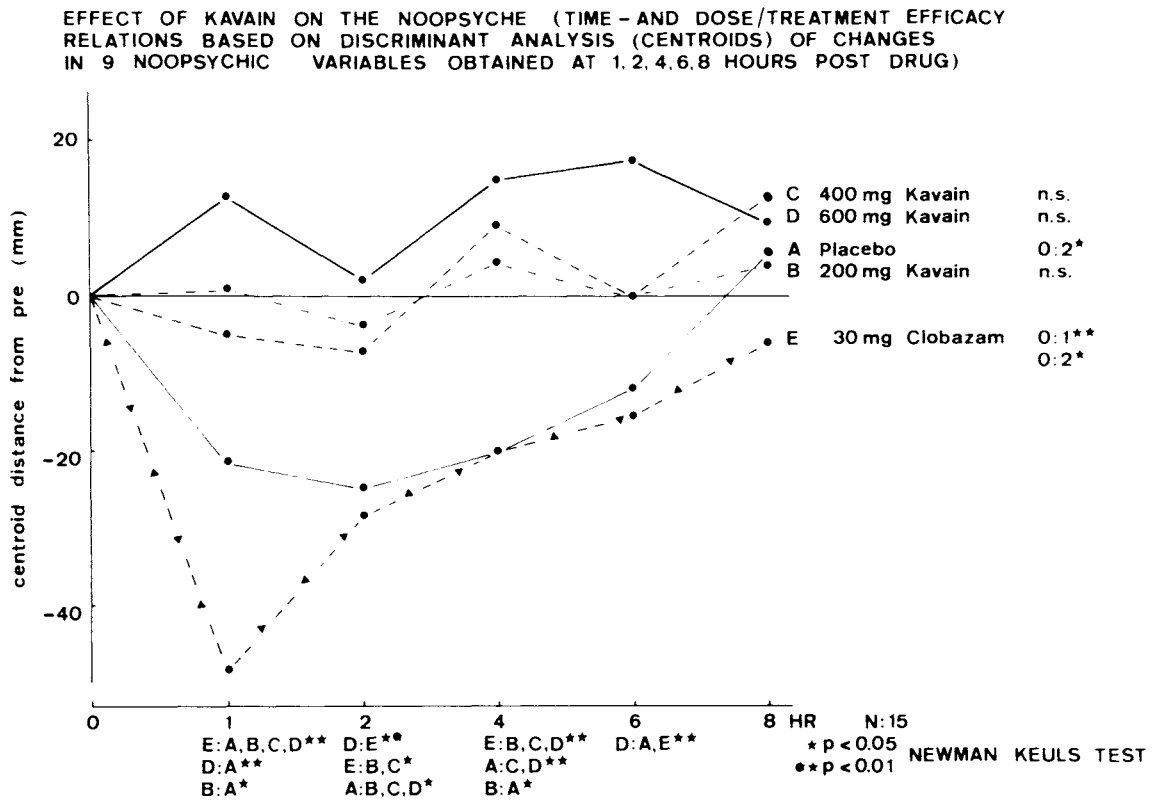

Figure 1. Effect of kavain on the noopsyche (time- and dose/treatment efficacy relations based on discriminant analysis (centroids) of changes in 9 noopsychic variables obtained at 1, 2, 4 6 and 8 hours after placebo, 200, 400 and 600 mg kavain and 30 mg clobazam; *n*:15). Time is shown in the abscissa, changes from the pre-treatment are indicated in the ordinate. As compared with pre-treatment, placebo induces a significant deterioration in the 2nd hour, 30 mg clobazam in the 1st and 2nd hour. In contrast, either no changes or even slight improvements in noopsychic performance occur after kavain. Thus, inter-drug comparison at various time points demonstrate significant superiority of all 3 doses of kavain over placebo as well as the reference compound

performance as compared with pre-treatment which differed from the placebo induced changes at the level of statistical significance between the 1st and 6th hour (Figure 1). However, also 400 mg kavain was significantly superior to placebo in the 2nd and 4th hour as was 200 mg in the 1st, 2nd and 4th hour. In contrast, 30 mg clobazam produced a deterioration of noopsychic performance in the 1st and 2nd hour as compared with pre-treatment (Figure 1). Thus, inter-group comparison by means of the Newman-Keuls test showed that 30 mg clobazam was significantly inferior to placebo in the 1st hour.

2. Noopsychic changes - univariate analysis

A. Correct calcuations in the Pauli-test demonstrated significant changes overtime and inter-drug differences in the 3-way ANOVA (Figure 2). In detail, we observed no significant changes after placebo, 400 and 600 mg kavain as compared with pre-treatment. There was an improvement of performance after 200 mg kavain which reached the level of statistical significance in the 8th hour ($p < 0{\cdot}05$, Newman-Keuls Test) while a deterioration occurred in the 1st hour after 30 mg clobazam ($p < 0{\cdot}01$). Inter-drug comparison showed a significant superiority of 200 mg kavain over placebo in the 1st and 2nd hour, of 400 mg in the 2nd hour and of 600 mg kavain in the 2nd and 4th hour, while clobazam was significantly inferior in the 1st and 6th hour. Moreover, 200 mg kavain were significantly superior to the reference compound in the 1st to the 8th hour, 400 mg in the 1st two hours and 600 mg also the 1st throughout the 8th hour.

B. *Evaluation of errors* in per cent of the total score in the Pauli-test showed significant changes over

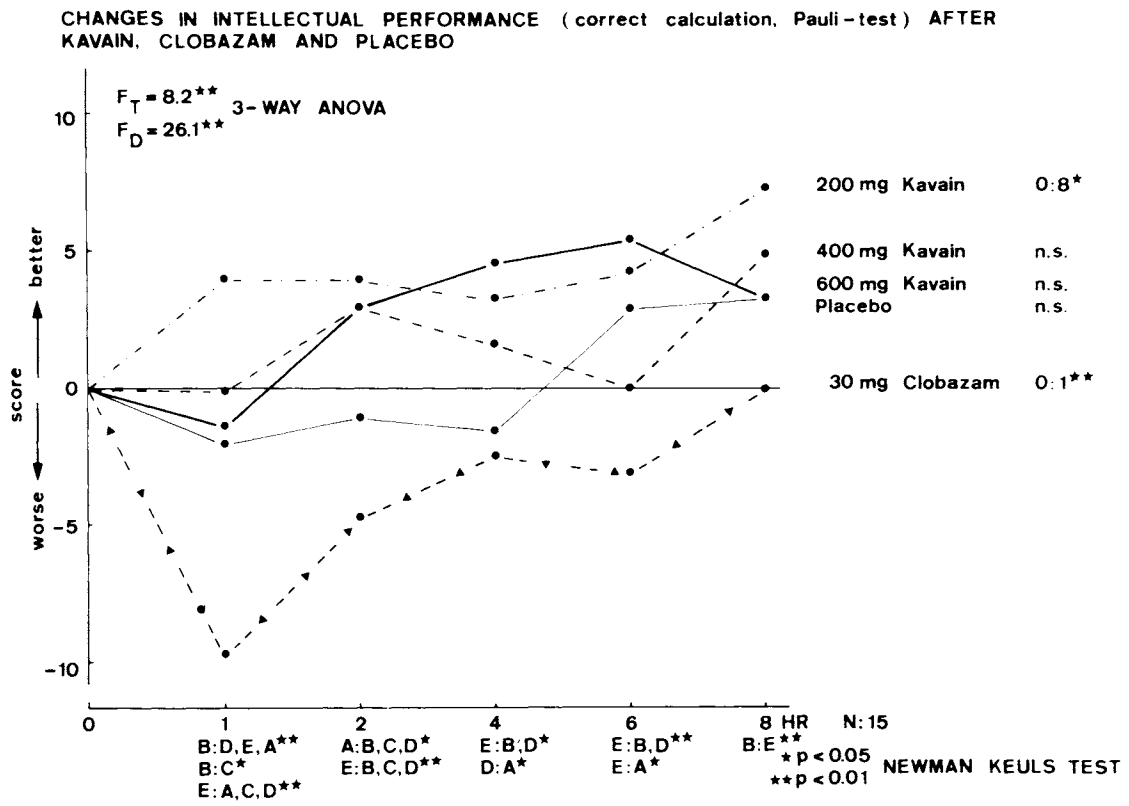

Figure 2. Changes in intellectual performance (based on correct calculations in the Pauli test) after placebo, 200, 400 and 600 mg kavain and 30 mg clobazam (n:15). Time is shown in the abscissa, changes from pre-treatment in the ordinate. Placebo induces only minimal alterations. An improvement can be seen after all 3 doses of kavain, while 30 mg clobazam produces opposite alterations

time as well as inter-drug differences in the 3-way ANOVA (Table 3). This was due to the fact that there was quite an increase in errors under placebo and 30 mg clobazam while opposite changes occurred after all three dosage of kavain. Thus, inter-drug comparison by means of the Newman-Keuls test demonstrated a significant superiority of all three dosage of kavain over placebo and 30 mg clobazam in the 2nd hour post-drug.

C. *Attention* as evaluated by means of the total score in the alphabetical cross-out test of Grünberger (1977) showed in the 3-way ANOVA significant changes over time as well as significant inter-drug differences. Detailed analysis of changes after each substance demonstrated only afer 30 mg clobazam significant changes in the 1st, 2nd and 4th hour as compared with pre-treatment ($p < 0{\cdot}01$, Newman-Keuls test), which reflected a decrease in attention. All the other substances showed either no changes or even a trend towards an improvement. Thus, inter-drug comparison by means of the Newman-Keuls test demonstrated a superiority of 400 mg kavain in the 4th and 6th hour over placebo and of 600 mg kavain in the 4th hour, while 30 mg clobazam were inferior between the 1st, 2nd and 4th hour. Moreover, 200 mg kavain were significantly superior to the reference compound between the 1st and 4th hour, the 400 mg dosage between the 1st and 6th hour and the 600 mg dosage between the 1st and 8th hour (Table 3).

D. *Concentration* as evaluated by means of errors in % of the total score of the alphabetial cross-out test of Grünberger demonstrated significant changes over the time and inter-drug differences in the 3-way ANOVA (Table 3). This was mostly due to the fact that under placebo and 30 mg clobazam there was a trend towards an increase of errors, while after 200 mg but also 600 mg kavain there was a

Table 3. Change in noopsychic variables after a single dose of 200, 400, and 600 mg Kavain and 30 mg Clobazam as compared with placebo in normals (N=15, 1, 2, 4, 6, 8 hrs post drug)

Variable	3-Way Anova		As compared with Placebo				As compared with 30 mg Clobazam		
	^{F}Time	^{F}Drug	200 mg Kavain	400 mg Kavain	600 mg Kavain	30 mg Clobazam	200 mg Kavain	400 mg Kavain	600 mg Kavain
Pauli-Test (Correct) ↑	8,2**	26,1**	$+_4$1, +2	+2	+2,4	=1,-6	++1, 2, 6,8	++1,2	++1,2, 6,8 +4
Pauli-Test (Errors %) ↓	3,9**	3,8**	-2	-2	-2		+2	+2	+2
Attention (Total Score) ↑	8,8**	25,5**		+4,6	+4	=1,2 ;-4	++1-4	++1-6	++1-4, +8
Concentration (Errors %)↓	4,0**	6,6**	-1,2		=1		-1		=1
Attention Variability ↓									
Numerical Memory (Score) ↑						-1	++1	+1	++1
Psychomotor Activity ↑ (Score)	4,8**	9,6**				=1	++1	++1	++1
Reaction Time (msec) ↓		4,8**			-1,8				++1
Reaction Time Task (Errors) ↓		9,7**	+2	++2-4		+6	-6	-1,6	=6

↓↑direction of improvement *p<0,05 +increase/-decrease in certain hours post drug $p < 0{,}065$ Newman Keuls-Test
**p<0,01 ++increase/-decrease in certain hours post drug $p < 0{,}01$

trend towards a decrease. Thus, 200 mg 600 mg kavain in the 1st hour. Moreover, 200 and 600 mg kavain were significantly superior to the reference compound in the 1st hour as well.

E. *Attention variability* did not show any significant findings.

F. *Short-term memory* as evaluated by the numerical memory test of Grünberger (1977) demonstrated no significant changes in the 3-way ANOVA. Detailed analysis of changes after each single substance showed a significant deterioration in memory in the 6th hour after 200 mg, in the 2nd hour after 400 mg kavain and in the 1st and 4th hour after 30 mg clobazam as compared with pre-treatment ($p < 0{\cdot}05$, Newman-Keuls Test). Inter-drug comparison showed that 30 mg clobazam was significantly inferior to placebo but also to all three doses of kavain in the 1st hour after drug administration.

G. *Fine motor activity test* (Grünberger 1977) demonstrated significant changes over time and inter-drug differences in the 3-way ANOVA (Table III). In detail, we observed a significant improvement of psychomotor performance in the 6th hour after 600 mg kavain and a deterioration in the 1st hour after 30 mg clobazam as compared with pre-treatment ($p < 0{\cdot}05$ and 0·01, respectively). Inter-drug comparison demonstrated that 30 mg clobazam was significantly inferior to placebo in the 1st hour but also to all 3 doses of kavain (Table 3).

H. *Reaction time (in msec)* as measured by means of the Viennese reaction time apparatus demonstrated significant inter-drug differences in the 3-way ANOVA (Table 3). This was due to the fact that 600 mg kavain showed a shortening of reaction time which was significantly superior to placebo which exhibited a trend towards a lengthening in the 1st as well as in the 8th hour (Table 3). Moreover, 600 mg kavian were also significantly superior to the reference compound as well as to the 400 mg dosage in the 1st hour and to the two other lower doses in the 8th hour.

I. *Errors in the reaction time task* showed significant inter-drug differences in the 3-way ANOVA (Table 3). In detail we observed an increase in errors in the 6th hour after 30 mg clobazam as compared with pre-treatment ($p < 0{\cdot}05$, Newman-Keuls test). Inter-drug comparison by means of the Newman-Keuls test demonstrated a significant inferiority of 30 mg clobazam to placebo in the 6th hour post drug but also to all three dosages of kavain. Already in the 1st hour 400 mg kavain were significantly superior to the reference compound.

J. Evaluation of *rigidity and perseveration* by means of a computer-assisted technique demonstrated based on a multivariate analysis of 14 test variables that no significant changes occurred after any of the 5 substances over time. There was a trend toward an increase of rigidity after 400 mg kavain as opposed to a trend towards a decrease in rigidity and increase in flexibility after 600 mg kavain. Indeed, there was a significant difference between these two dosages in the 8th hour post-drug with the 400 mg dosage differing also from placebo (Newman-Keuls test, $p < 0.05$). Concerning detailed changes in the 14 variables, the most significant findings were observed in regard to speed of pressing 10 buttons in random order with the left index finger within one minute (Figure 3). As compared with pre-treatment, there was a significant increase in the 6th hour after 600 mg kavain while a decrease occurred in the 2nd hour after 30 mg clobazam ($p < 0{\cdot}05$ and 0·01, Newman-Keuls test, respectively). Inter-drug comparison by means of the Newman-Keuls test demonstrated that, as compared with placebo, a decrease occurred after 30 mg clobazam in the 2nd hour, while an increase occurred in the 4th and 6th hour after 600 mg kavain and in the 6th hour after 400 mg kavain. The reference compound was significantly different from kavain at all times. Speed of the right hand showed only a significant decrease as compared with placebo in the 2nd hour after 30 mg clobazam but no significant changes after kavain. The redundancy of the first order (flexibility in pressing buttons) showed a significant improvement in the left hand after 600 mg kavain as compared with placebo at all times and also compared with the pre-treatment value whereas this was not seen with the right hand.

3. *Thymopsychic changes - multivariate analysis*
A multivariate analysis by means of MANOVA and discriminant analysis considering changes in four thymopsychic variables at all times post-drug (1, 2, 4, 6 and 8 hours) and after all five substances demonstrated a significant deterioration as compared with pre-treatment 6 hours after placebo, 1 and 8 hours after 400 mg kavain, 2 and 4 hours after 600 mg kavain and 1, 2 and 6 hours after 30 mg clobazam, while there was a significant improve-

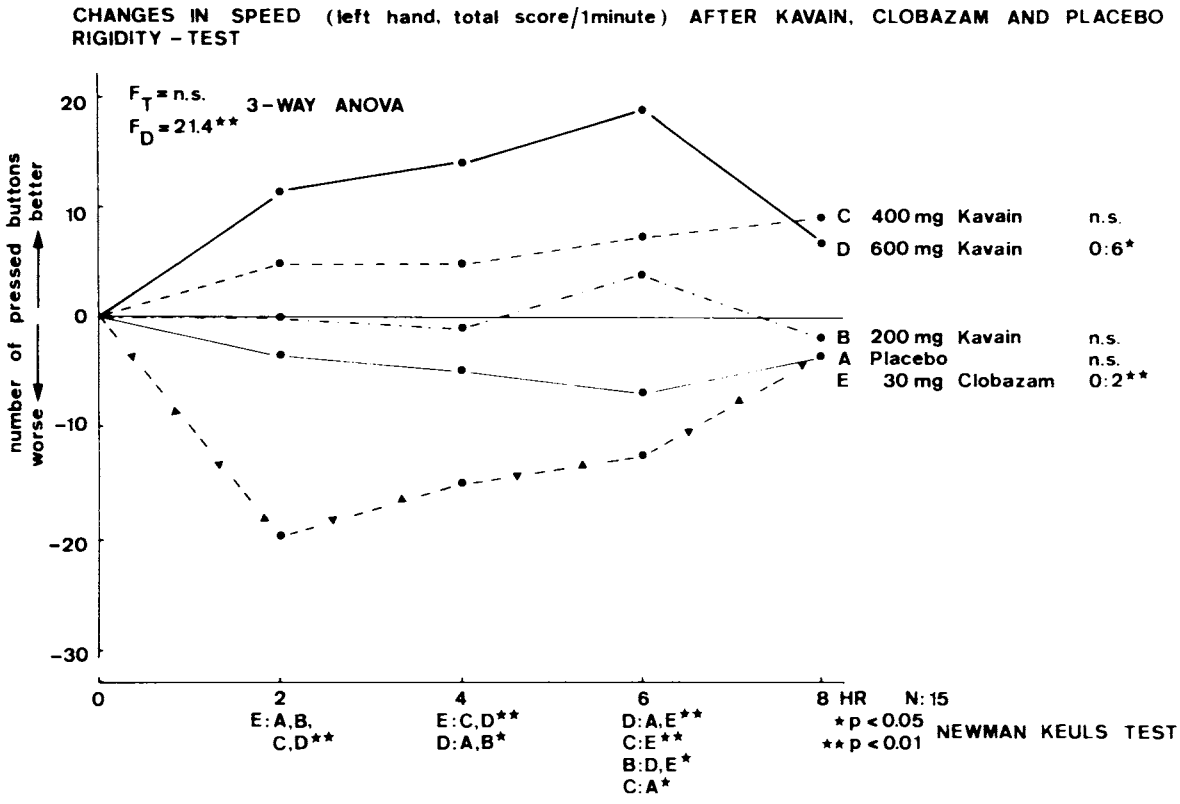

Figure 3. Changes in speed of pressing ten buttons within one minute (rigidity test) after placebo, 200, 400 and 600 mg kavain as well as 30 mg clobazam (n:15). Time is shown in the abscissa, changes in the number of pressed buttons as compared with pre-treatment are indicated in the ordinates. Placebo induces only minimal alterations. Kavain produces a dose-dependent increase in speed while 30 mg clobazam shows a decrease

ment 2 hours after 200 mg kavain (Figure 4). Inter-drug comparison at each single time point demonstrated a significant superiority of 200 mg kavain over placebo in the 4th and 6th hour, while 400 mg kavain were found significantly interior to placebo in the 1st, 2nd and 8th hour, 600 mg kavain in the 2nd, 4th and 8th hour and 30 mg clobazam in the last and 2nd hour. Moreover, 200 mg kavain were significantly superior to the reference compound from the 1st to the 6th hour, 400 mg kavain in the 1st and 2nd but also in the 8th hour and 600 mg kavain in the 1st, 2nd and 8th hour. Whereas, the time of the maximal drug effect of kavain was in the 2nd hour, that of 30 mg clobazam was in the 1st hour.

4. *Thymopsychic changes – univariate analysis*

A. *Drive* as evaluated by means of 100 mm visual analogue scale (VAS) showed in the 3-way ANOVA significant changes over time (Fd = 3·8, $p < 0{\cdot}01$), as well as significant inter-drug differences (Fd = 22·7, $p < 0{\cdot}01$). Detailed analysis of changes after each single substance demonstrated a deterioration of drive in the 1st and 2nd hour after 30 mg clobazam as compared with pre-treatment ($p < 0{\cdot}01$, Newman-Keuls test) (Figure 5). Evaluation of inter-drug differences by means of the Newman-Keuls test at each single time epoch demonstrated a significant improvement of 200 mg kavain as compared with placebo in the 2nd and 6th hour while a significant deterioriation after 30 mg clobazam in the 1st and 2nd hour. Moreover, in the 1st and 2nd hour all three kavain doses were significantly superior to the reference compound which in the 4th and 6th hour was only true for the low dosis.

B. *Sedation* as rated by the subject themselves by means of a 100 mm visual analogue scale (VAS) demonstrated significant changes over time and

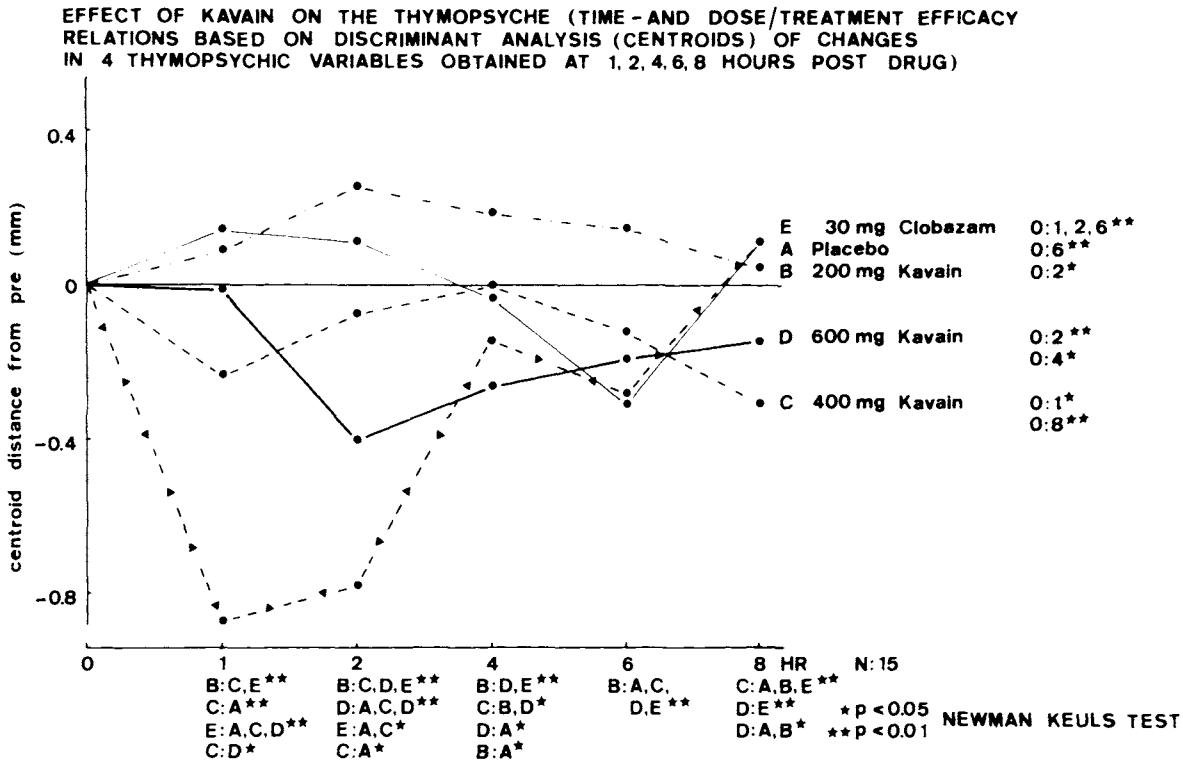

Figure 4. Effect of kavain on the thymopsyche (time- and dose/treatment efficacy relations based on changes in 4 thymopsychic variables obtained at 1, 2, 4, 6, and 8 hours after placebo, 200, 400, and 600 mg kavain as well as 30 mg clobazam). Placebo induces only minimal alterations, while the lowest dosage of kavain (200 mg) produces an activation, 30 mg clobazam induces deactivation

inter-drug differences in the 3-way ANOVA (Table 4). Evaluation of changes after each single substance as compared with baseline demonstrated an increase in sedation in the 1st and 2nd hour after 30 mg clobazam. Inter-drug comparison thus showed a significant difference between 30 mg clobazam inducing sedation and all the other substances showing no changes or an activation in the 1st and 2nd hour. The latter was seen after 200 mg kavain which was significantly different from 30 mg clobazam in the 1st throughout the 6th hour.

C. *Mood* as evaluated by means of a 100 mm visual analogue scale (VAS) showed in the 3-way ANOVA significant inter-drug differences (Table 4). As compared with pre-treatment, mood deteriorated in the 2nd hour after 600 mg kavain and in the 1st and 2nd hour after the reference compound. Inter-drug comparison showed 400 mg kavain significantly different from placebo in the 8th hour, 600 mg in the 2nd, 4th and 8th hour and 30 mg clobazam in the 1st and 2nd hour (with the active drugs producing more deterioration in mood than placebo). On the other hand, 200 mg kavain were significantly superior to the reference compound in the 1st and 2nd hour, while 400 mg wer so in the 2nd hour. However, 600 mg were inferior in the 4th hour (Table 4).

D. *Affectivity* (affective resonance) as evaluated by a 100 mm VAS showed in the 3-way ANOVA significant inter-drug differences (Table 4). As compared with pre-treatment, 30 mg clobazam produced a decrease in affectivity in the 1st and 2nd hour ($p < 0{\cdot}01$, Newman-Keuls test). Inter-drug comparison showed that 30 mg clobazam was significantly different from all the other 4 substances at these times, as the latter did not include any changes.

E. *Well-being* as evaluated by means of the vo Zerssen Bf-scale demonstrated significant inter-drug differences in the 3-way ANOVA (Table 4). As

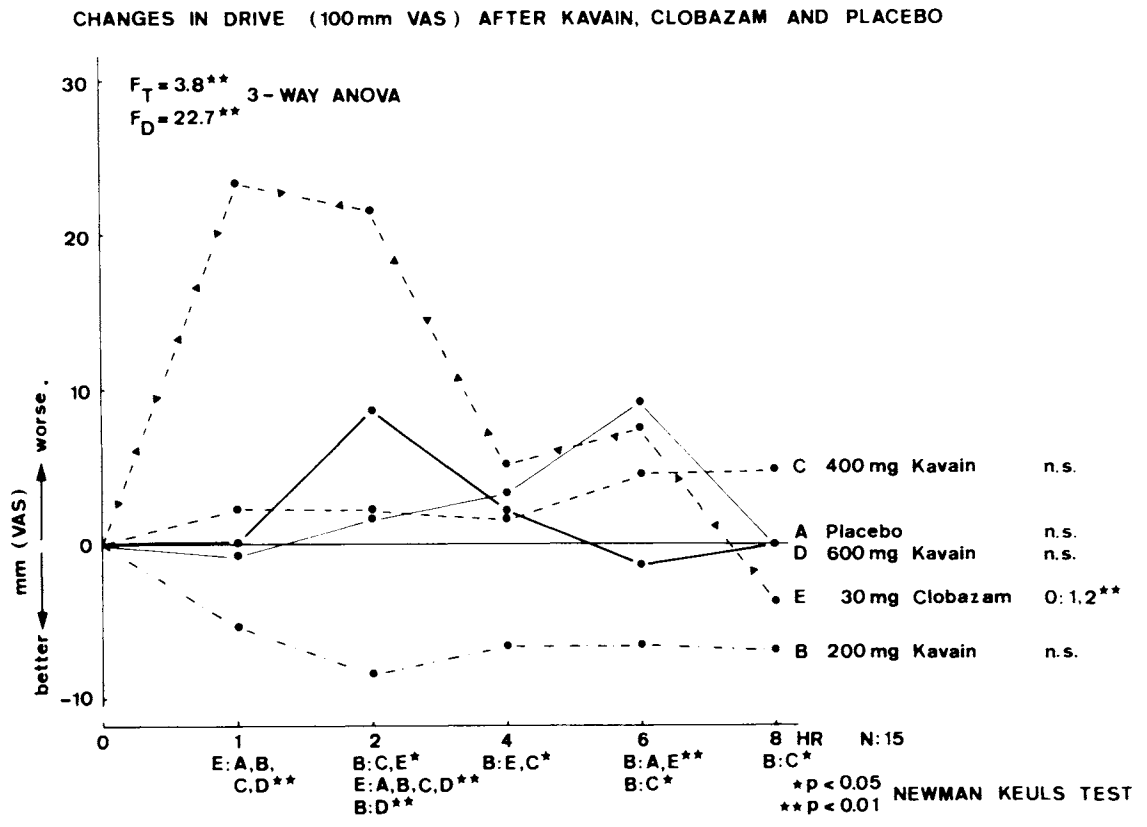

Figure 5. Change in drive (100mm VAS) after kavain, clobazam and placebo (n:15). While 200 mg kavain improves drive, 30 mg clobazam deteriorates it

compared with pre-treatment, 30 mg clobazam produced a deterioration of well-being in the 2nd hour ($p < 0{\cdot}01$, Newmann-Keuls). Inter-drug comparison showed that this deterioration was significantly different from the slight improvement after placebo in the 2nd hour. However, also all three doese of kavain were significantly superior to the reference compound at that time (Table 4).

F. The *total score of the semantic differential polarity profile* (including the dimensions: subjectively experienced wakefullness, mood, concentration and extraversion) demonstrated significant inter-drug differences (Table 4). As compared with pre-treatment, clobazam produced a deterioration in the 2nd, 4th and 6th hour. Inter-drug comparison demonstraed that clobazam induced a significant deterioration as compared with placebo in the 2nd hour, while 200 mg kavain produced a significant improvement. Further, 200 mg kavain were significantly superior to the reference compound in the 2nd and 4th hour, 400 mg in the 2nd hour and 600 mg in the 2nd and 6th hour.

5. *Psychophysiological findings – multivariate analysis*

A multivariate statistic analysis by means of the MANOVA and dicriminant analysis considering changes in 17 psychophysiological variables obtained at 2, 4, 6, 8 hours after all five substances demonstrated a significant improvement 6th hours after 200 mg and 600 mg kavain as compared with baseline (Figure 6). Inter-drug comparison showed that 30 mg clobazam were significantly different from placebo, 200 and 400 mg kavain in the 2nd hour post drug, as the former induced a slight deterioration, the latter a slight improvement. Moreover, 200 mg and 600 mg kavain were significantly different from the reference compound in the 6th hours.

Table 4. Changes in Thymopsychic variables at different times after a single dose of 200, 400 and 600 mg Kavain and 30 mg Clobazam as compared with Placebo in normals (N=15)

Time of Testing	Variable	3-Way Anova		As compared with Placebo				A compared with 30 mg Clobazam		
		^{F}Time	^{F}Drug	200 mg Kavain	400 mg Kavain	600 mg Kavain	30 mg Clobazam	200 mg Kavain	400 mg Kavain	600 mg Kavain
	Drive (VAS)↓	3,8**	22,7**	–2, =6			++1,2	=1,2,6 –4	=1,2	=1,2
	Sedation (VAS)↓		16,2**				++1,2	=1,2 –4,6		
	Mood (VAS)↑		12,1**		–8	=2,–4,8	=1,2	++1,2	+2	–4
	Affectivity (VAS)↑		5,6**				=1,2	++1,2	+1,++2	+½⅓1,+2
	Well-Being (BF-S)↓		7,1**				++2	++2	++2	++2
	Semenatic Differential↓									
	Polarity Profile (Score)		13,4**	–2			++2	=2,4	=2	=2,–6

↓↑direction of improvement *$p<0,05$ +increase/-decrease at $p < 0,05$ Newman Keuls-Test
**$p<0,01$ ++increase/-decrease at $p < 0,01$

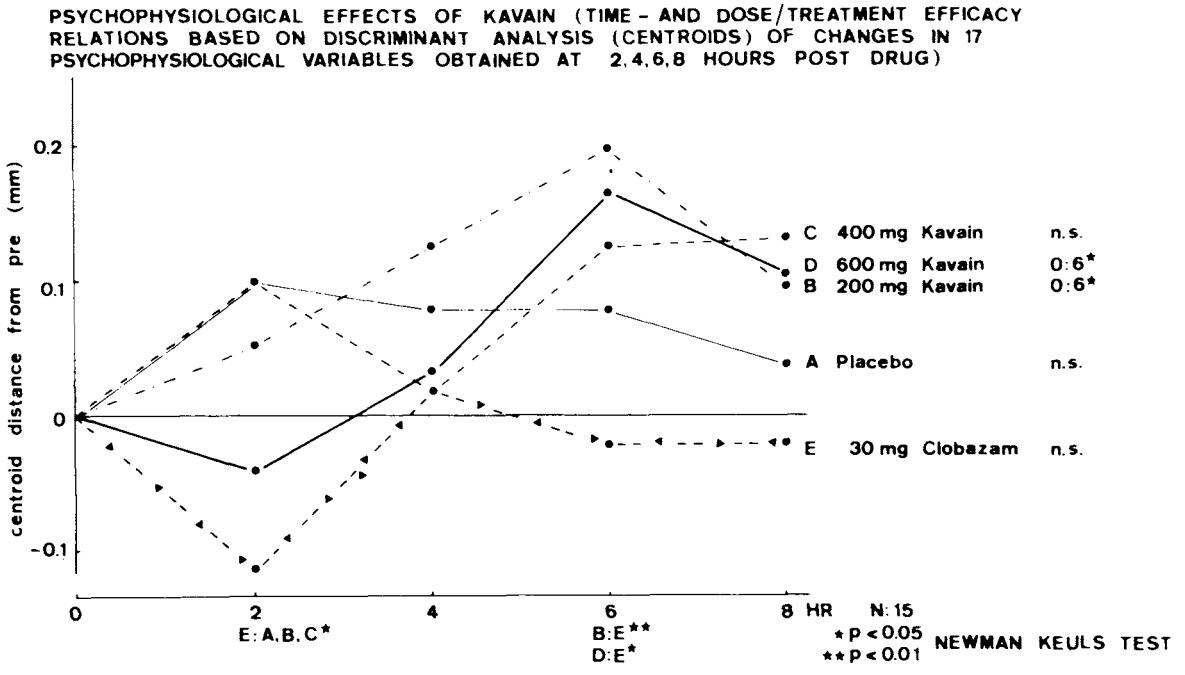

Figure 6. Psychophysiological effects of kavain (time- and dose-treatment efficacy relations based on changes in 17 psychophysiological variables obtained in the 2nd, 4th, 6th, and 8th hour after placebo, 200, 400 and 600 mg kavain as well as 30 mg clobazam). Only 30 mg clobazam produces in the 2nd hour post drug changes significantly different from placebo

6. *Psychophysiological findings - univariate analysis*

A. *Critical flicker frequency* (CFF, descending threshold) showed significant changes over time and inter-drug differences in the 3-way ANOVA (Table 5). As compared with pre-treatment, CFF increased in the 8th hour after 400 mg kavain while it decreased at all times after 30 mg clobazam. Inter-drug comparison showed a significant difference of 400 mg kavain (producing a CFF increase) in the 6th and the 8th hour from 30 mg clobazam (producing a decrease). The reference compound was significantly different from placebo in the 2nd and 6th hour. Kavain produced a CFF increase as compared with the reference compound in the 2nd to the 6th hour after 200 mg, as well as in the 2nd to the 8th hour after 400 mg and 600 mg kavain.

B. *Skin conductance level* (SCL in μmhos) showed significant inter-drug differences in the 3-way ANOVA (Table 5) which was due to the fact that 200 mg kavain increased skin conductance in the 8th hour both as compared with placebo and the reference compound. The increase was also significant as compared with pre-treatment ($p < 0{\cdot}05$, Newman-Keuls).

C. *Number of SCL - fluctuations* showed also significant inter-drug differences in the 3-way ANOVA (Table 5) which was due to the fact that 30 mg clobazam decreased the number of fluctuations as compared with placebo and all 3 doses of kavain in the 8th hour.

D. *Pupillary diameter* as measured by means of a micro-processor-assisted pupillometer demonstrated significant changes over time and inter-drug differences in the 3-way ANOVA (Table 5). As compared with pre-treatment, pupil size increased in the 8th hour after placebo, further in the 4th to the 8th hour after 200 mg kavain and decreased in the 2nd hour after 30 mg clobazam (Figure 7). Inter-drug comparison showed a narrowing of the pupil in the 2nd and 6th hour after 30 mg clobazam as compared with placebo which was significantly different from 200 mg kavain exhibiting an increase in the

Table 5. Changes in psychophysiological variables after a single dose of 200, 400 and 600 mg Kavain and 30 mg Clobazam as compared with Placebo in normals (N=15)

Group	Variable 0,2,4,6,8 H	3-Way Anova		As compared with Placebo				A compared with 30 mg Clobazam		
		^{F}Time	^{F}Drug	200 mg Kavain	400 mg Kavain	600 mg Kavain	30 mg Clobazam	200 mg Kavain	400 mg Kavain	600 mg Kavain
CFF	Descending Threshold (HZ)	32,2**	33,5**		+6, ++8		=2-6	+±2-6	++2,6,8	++2-6,+8
Skin	SCL (μmhos)		5,1**	+8				+8	+2	
	SCL-Fluctuations (Numbers)		4,8**				-8	+8	++8	+8
	Pupillary Diameter (mm)	18,4**	16,5**				-2,6	++2-6	++6	++6
	Pupillary-Fluctuations (Numbers)									
	Baseline (mm) PR-8	6,2**	7,8**		-2	=2	=2	+2-6		
	Maximal Constriction (mm) PR-MC	8,3**	12,9**		-2	-2	-2	++2,4,+6		
Dynamic	Change (mm) PR-AC									
Pupil:	Change (%) PR-RC									
1st	Latency (sec) PR-L		10,2**	=4,-6,8		-8		=4		
Stimulus	Decening Time (sec) PR-DT	3,7*	9,8**	+4,8	+8			+2, ++4	+4	+2,4
	Half-Recovery Time (sec) PR-RI		5,2**							
	Construction Speed (PR-AC/PR-DT)		8,9**	-2,6,8		-2		+4		
	Recovery Speed (1/2 PR-AC (PR-RI)		10,9**	+6	++2,6	+6		++4		
	Area (PR-RT *PR-RC)		2,6*				-2			
	Time to Peak Effect (PR-L + PR-DT)		14,7**	-8	=2,6, -4	-6	=2-6			
	Time-Quoitent (PR-DT/PR-RT)									

*$p<0,05$ +increase/-decrease at $p<0,05$ Newman Keus-Test
**$p<0,01$ ++increase/-decrease at $p<0,01$

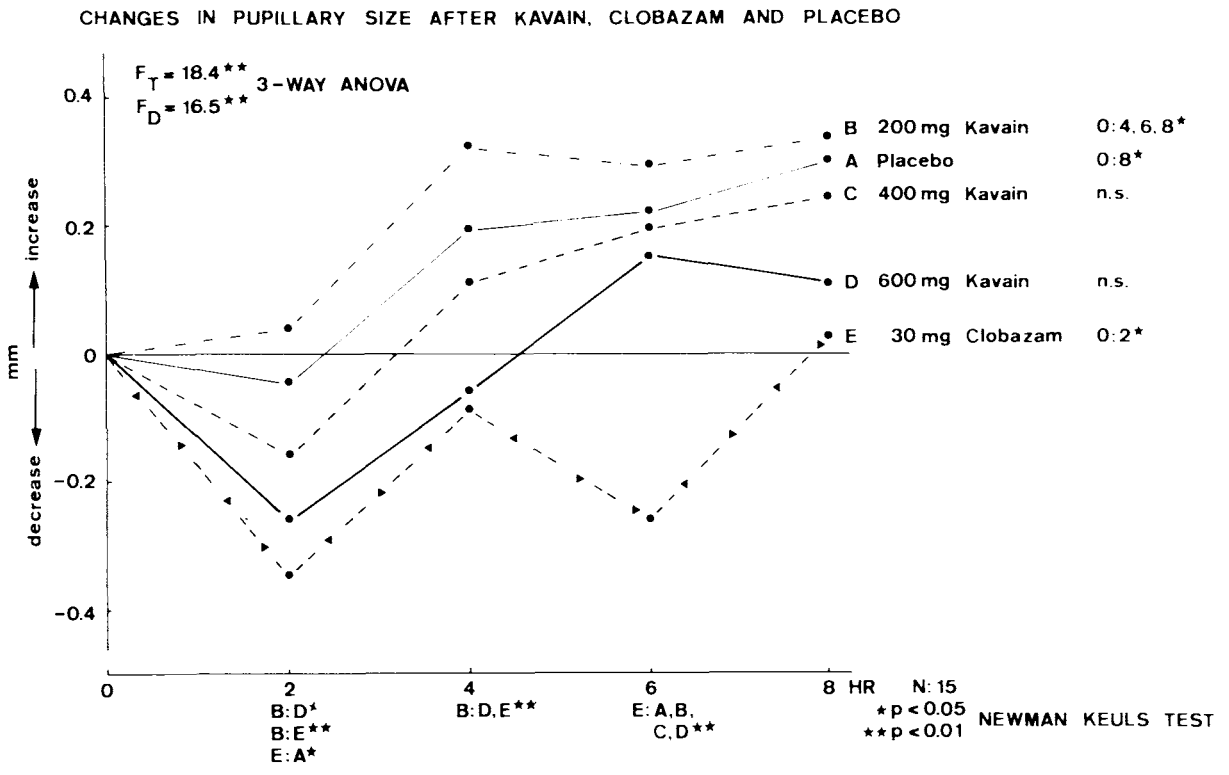

Figure 7. Changes in the pupil size after placebo, 200, 400 and 600 mg kavain and 30 mg clobazam (n:15). Pupil size decreases - as compared with placebo - only after 30 mg clobazam at a level of statistical significance.

2nd throughout the 6th hour. In the 6th hour all 3 kavain doses differed from the reference compound.

E. *Pupillary fluctuations* were not altered by any of the compounds.

F. *Dynamic pupillometry* demonstrated changes in several variables. *Baseline recordings* before the 1st evoked pupillary response showed both significant changes over time and inter-drug differences in the 3-way ANOVA (Table 5). There was an increase in pupil size in the 4th hour after 200 mg kavain. Inter-drug comparison demonstrated in the 2nd hour a decrease after 400 mg and 600 mg kavain as well as the reference compound as compared with placebo. Moreover, 200 mg kavain differed from the reference compound in the 2nd throughout the 6th hour as it induced an increase in pupil size. The value of the *maximal constriction* showed also significant changes over time and inter-drug differences (Table 5). As compared with pre-treatment, 200 mg kavain produced an increase in the 4th and 8th hour ($p < 0{\cdot}05$, Newman-Keuls). Inter-drug comparison showed a significant decrease in the 2nd hour after 400 and 600 mg kavain and 30 mg clobazam as compared with placebo. 200 mg kavain differed from the reference compound from the 2nd to the 6th hour. The *latency* of the pupillary reaction showed significant inter-drug differences (Table 5) which was due to the fact the 200 mg dosage of kavain significantly shortened latency in the 4th throughout the 8th hour, being significantly different from all the other compounds in the 4th hour as well. However, also the highest dosage of kavain shortened latency in the 8th hour. The reference compound produced a trend towards lengthening. *Descending time* showed significant changes over time and inter-drug differences (Table 5). In detail, descending time increased in the 4th and 8th hour after 200 mg kavain while after 400 mg kavain this was observed in the 8th hour. In contrast, the reference compound shortened descending

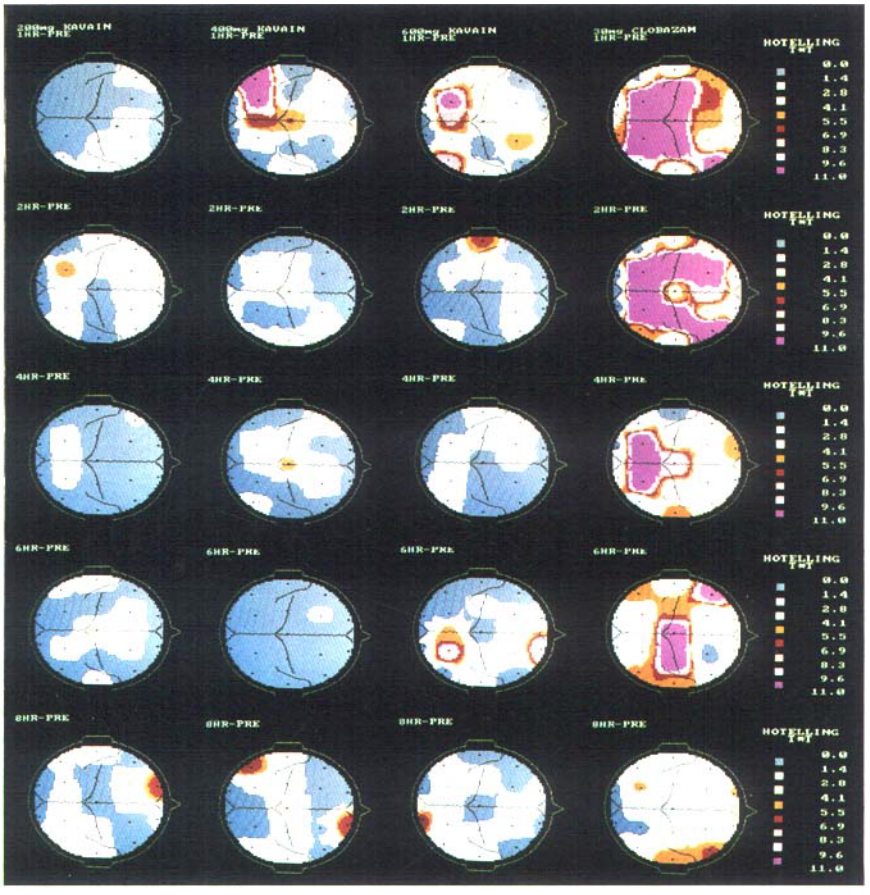

PLATE 1

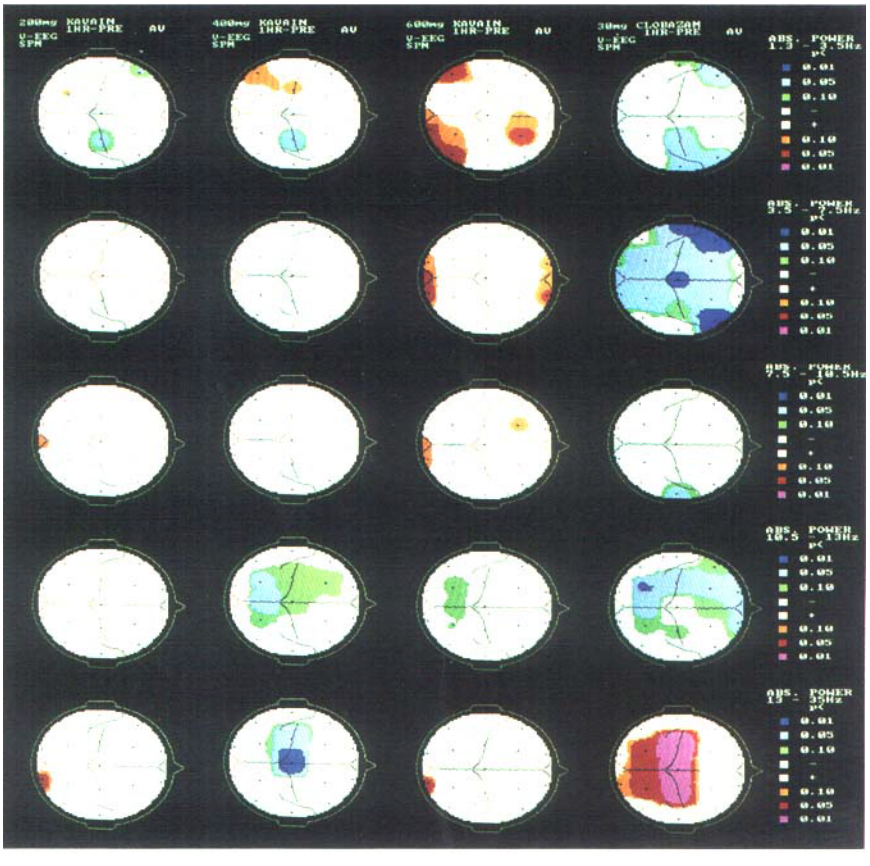

PLATE 2

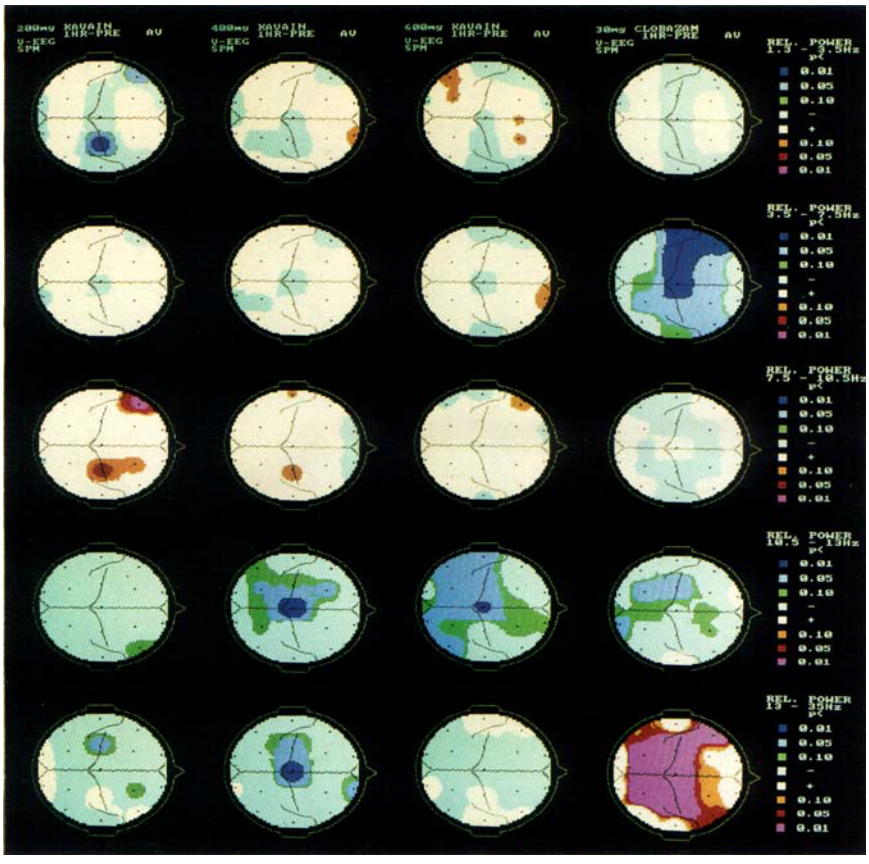

PLATE 3

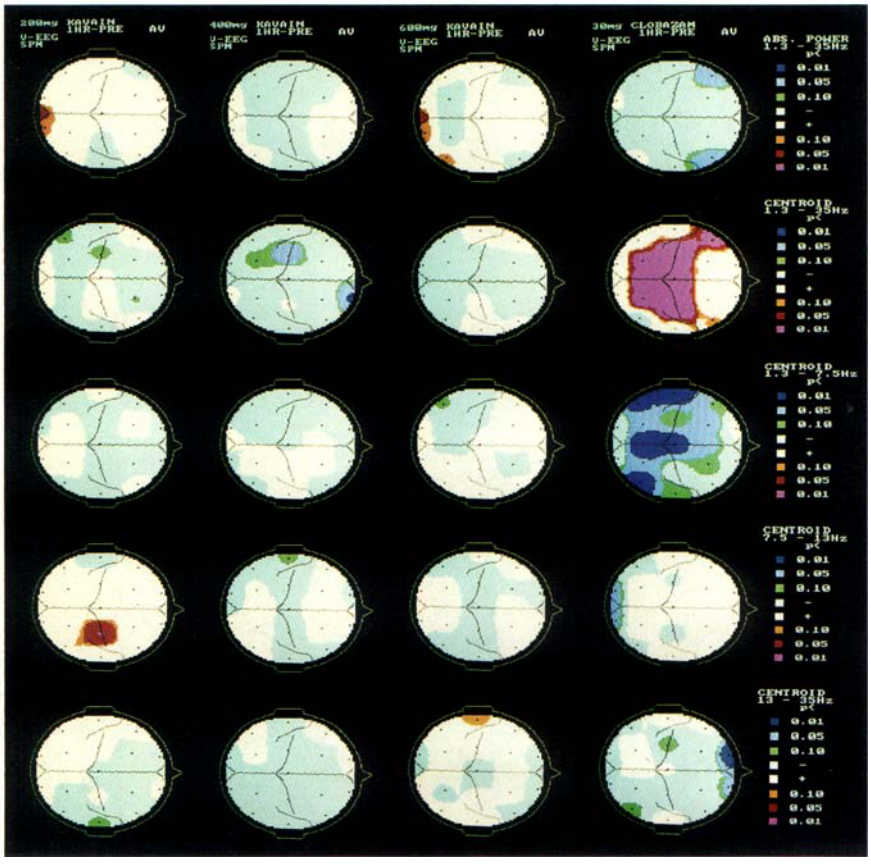

PLATE 4

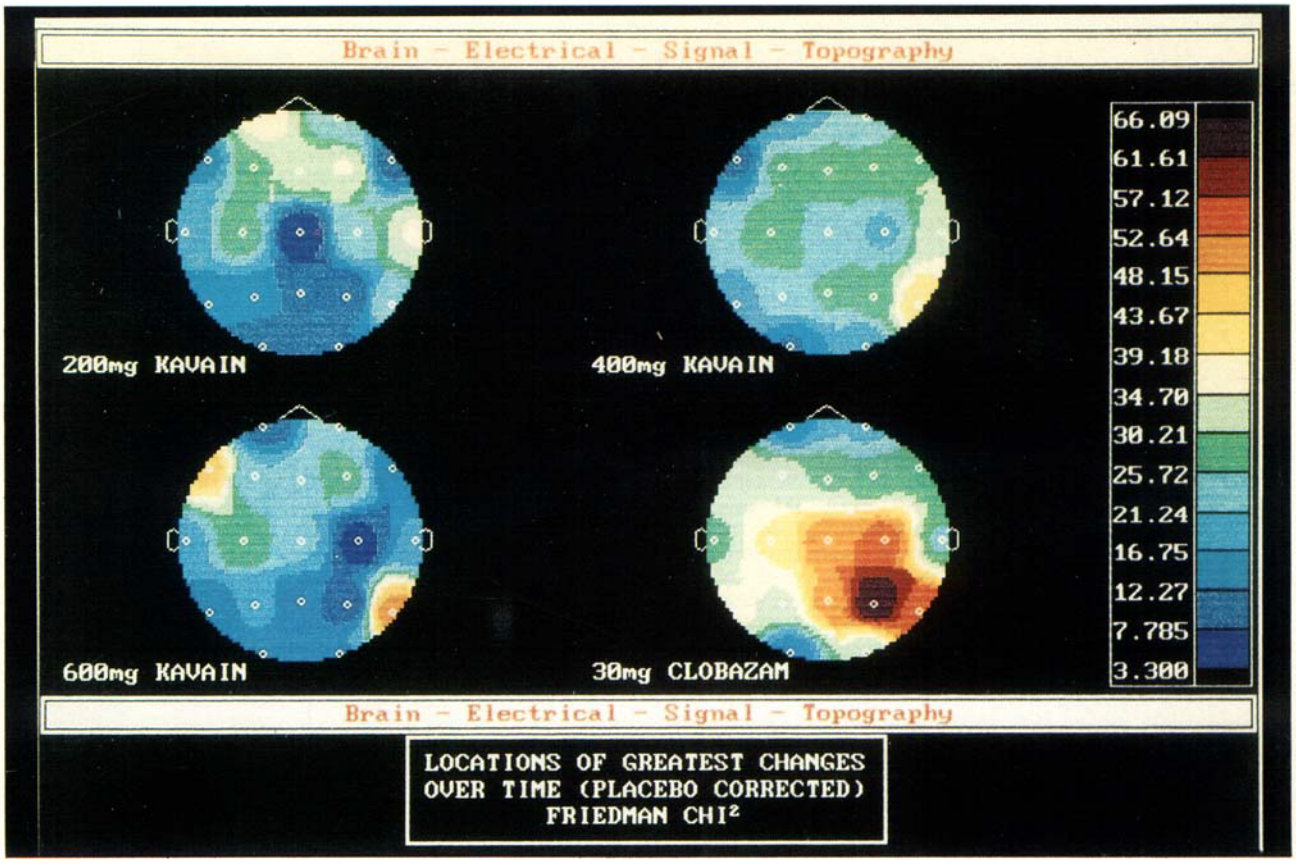

PLATE 5

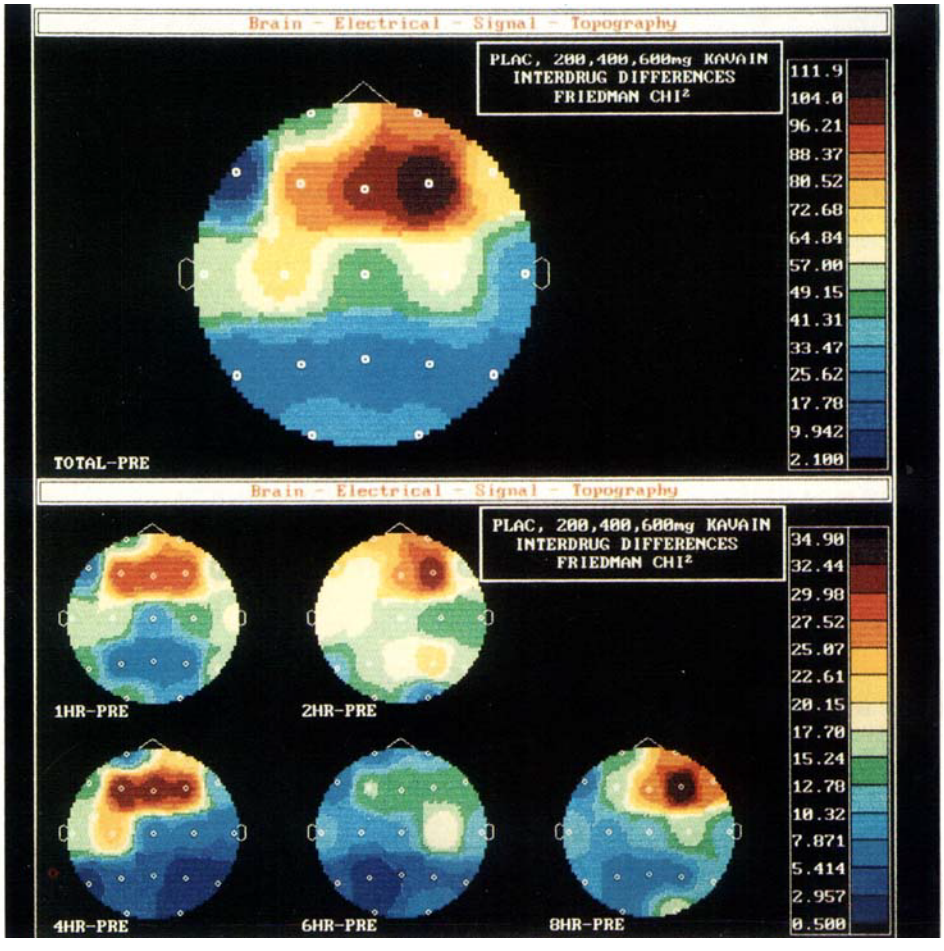

PLATE 6

Plate 1. Brain maps showing differences between drug-induced and placebo-induced central effects after 200, 400, 600 mg kavain and 30 mg clobazam (from the left to the right column) at hours 1 (top row), 2, 4, 6, and 8 (bottom row). Images are based on Hotelling T^2 obtained from multivariate tests in repeated measures ANOVA on the relative power of the nine frequency bands [ln (power %/(100-power %)) transformation] for each electrode (V-EEG, n = 15). Significant T^2: larger than 2·96 = $p < 0{\cdot}10$, larger than 4·10 = $p < 0{\cdot}05$ and larger than 7·98 = $p < 0{\cdot}01$. Kavain produced dose-dependent changes as compared with placebo mostly in the 1st and 2nd but also in the 8th hour, while 30 mg clobazam produced marked and highly statistically significant changes over large areas of the brain with a first peak in the 1st and a second peak in the 6th hour.

Plate 2. Maps of topographic pharmaco-EEG changes in absolute power of the delta (1·3–3·5 Hz), theta (3·5–7·5 Hz), slow alpha (7·5–10·5 Hz) fast alpha (10·5–13 Hz) and beta (13–35 Hz) activities (top to bottom rows) after 200 mg, 400 mg, 600 mg kavain and 30 mg clobazam (from the left to the right column) as compared with placebo at the 1st hour post drug (V-EEG, n = 15). Each significance probability map (SPM) represents the result of a statistical comparison by t-test of drug-induced and placebo-induced changes. The vertex view shows nose to the right, occiput to the left, left ear on the top, and right ear on the bottom. Electrode positions are indicated by black dots. Eight-color scales represent drug-induced changes based on t-values expressed in p-values (lilac, increase at $p < 0{\cdot}01$; red, increase at $p < 0{\cdot}05$; ochre, increase at $p < 0{\cdot}10$; pale yellow, trend toward increase; pale green, trend toward decrease; bright green, decrease at $p < 0{\cdot}10$; light blue, decrease at $p < 0{\cdot}05$; dark blue, decrease at $p < 0{\cdot}01$). While kavain produces a dose-dependent increase of absolute power in the delta, theta and alpha 1 band as well as a decrease in alpha 2 and beta power, 30 mg clobazam produces a decrease of absolute power in the 1·3–13 Hz activities and an increase in beta power.

Plate 3. Maps of topographic pharmaco-EEG changes in relative power of the delta (1·3–3·5 Hz), theta (3·5–7·5 Hz), slow alpha (7·5–10·5 Hz), fast alpha (10·5–13 Hz) and beta (13–35 Hz) activities (top to bottom rows) after 200, 400, 600 mg kavain and 30 mg clobazam (from the left to the right column) as compared with placebo in the 1st hour post-drug (V-EEG, n = 15). For technical description of the pharmaco-EEG maps and the 8 colour scale see Plate 2. Kavain produces in the low dosage a decrease, in the higher dosage a trend towards an increase of delta activity. Alpha 1 activity is enhanced by all 3 dosages, alpha 2 and beta activity dose-dependently attenuated. In contrast, 30 mg clobazam produces a significant attenuation of theta and alpha 2 activity and an augmentation of beta activity.

Plate 4. Maps of topographic pharmaco-EEG changes in total power (absolute power 1·3–35 Hz), centroid of the total activity (1·3–35 Hz) as well as the centroid of the combined delta/theta, alpha and beta frequencies (top to bottom rows) after 200, 400, 600 mg kavain and 30 mg clobazam (from the left to the right column) as compared with placebo at the 1st hour post drug (V-EEG; n = 15). For technical description of the pharmaco-EEG maps and the 8 colour scale see Plate 2. While kavain produces a slight increase of total power, 30 mg clobazam attenuates it. On the other hand, the centroid is slowed down by kavain and accelerated by clobazam. The centroid of the combined delta/theta is markedly slowed down by 30 mg clobazam but not by kavain which accelerates specifically in the lower doses the alpha centroid.

Plate 5. Locations of greatest changes over time after 200 mg, 400 mg, 600 mg kavain and 30 mg clobazam based on the x^2 values of the Friedman's rank ANOVA of placebo-corrected changes in all 28 EEG variables obtained at the hours 1, 2, 4, 6, and 8 from all leads. The colour key indicates x^2-values. While kavain produces more changes over anterior than posterior areas 30 mg clobazam is more active over central and parietal brain regions with a slight accentuation of the right hemisphere.

Plate 6. Locations of greatest difference between placebo, 200, 400 and 600 mg kavain based on Friedman's rank ANOVA of changes in 28 EEG variables obtained from all leads in different time period. The colour key indicates x^2 values. As can be seen, most differences between placebo- and kavain-induced changes are observed over anterior parts of the brain specifically over the right frontal regions.

time thus differing in the 4th hour from all 3 doses of kavain and in the 2nd hour from the 200 and 600 mg dosage.

Time to peak effect showed significant inter-drug differences as compared with placebo (Table 5). There was a significant shortening in the 8th hour after 200 mg, in the 2nd throughout the 6th hour after 400 mg, in the 6th hour after 600 mg kavain as well as in the 2nd throughout the 6th hour after 30 mg clobazam. The amplitude of the pupillary response did not change significantly. The constriction speed showed significant inter-drug differences (Table 5), as there was a decrease as compared with placebo in the 2nd, 6th and 8th hour after 200 mg kavain and in the 2nd hour after 600 mg kavain. 200 mg kavain differed also from the reference compound in the 4th hour. The half recovery time showed also significant inter-drug differences (Table 5) although a detailed analysis by means of the Newman-Keuls test did not exhibit anymore significant changes. The half recovery time multiplied by amplitude changes (in per cent of pretreatment values) showed only minimal differences between the substances (Table 5) as there was a significant decrease in the 2nd hour after 30 mg clobazam as compared with placebo. The time quotient did not show significant findings in the 3-way ANOVA. Finally, the recovery speed showed significant inter-drug differences (Table 5), as it increased in the 6th hour after all 3 doses of kavain as well as in the 2nd hour after the middle dose. 200 mg kavain was also significantly different from clobazum in the 4th hour.

Clinical findings

Pulse, systolic and diastolic blood pressure did not exhibit any clinically relevant changes after any of the 5 substances. There were no statistically significant differences between placebo and the active compounds nor between the active compounds themselves (Multiple Wilcoxon tests).

Somatic findings and side effects were observed in 7, 5, 6, 8 and 15 out 15 subjects after the administration of placebo, 200 mg, 400 mg, and 600 mg kavain as well as 30 mg clobazam, respectively. In detail, after placebo 6 subjects complained about mild to moderate tiredness and 2 about headaches. After 200 mg kavain 5 subjects complained about mild to moderate tiredness, after 400 mg 6 subjects, after 600 kavain 7 subjects. One of the latter was markedly tired, while another felt activated in the 2nd hour post-drug (and only later became tired). Two subjects noted slight to moderate dizziness in the 1st and 2nd hour after 600 mg kavain. After 30 mg clobazam 12 out of 15 subjects reported mild to marked tiredness, 7 of dizziness, 5 about giddiness, 1 about muscle relaxation, 1 about lack of drive and blurred vision on his right eye as well as lack of concentration and another one weakness.

DISCUSSION

Our double-blind, placebo-controlled EEG brain mapping studies with kavain demonstrated that the drug exerted, as compared with placebo, a significant effect on the human central nervous system (CNS) which differed in type, extent, time course and location from the reference compound 30 mg clobazam. Type and degree of kavain-induced EEG changes were dependent on the dosages. With increasing doses, kavain produced an augmentation of delta, theta and slow alpha activity, while fast alpha and beta activity decreased. These subtle changes were in contrast to marked changes after 30 mg clobazam characterized by a decrease in delta, theta, alpha 1, and alpha 2 activity while beta activity was markedly augmented. Further differences were seen in regard to total power which showed a small increase after all 3 doses of kavain while a decrease with clobazam. Moreover, the centroid slowed down after all 3 doses of kavain, but was markedly accelerated over almost the whole brain after clobazam. Analysis of the centroid of the combined delta/theta activity showed only slight changes after kavain but a marked slowing after 30 mg clobazam. The alpha centroid was slightly augmented by the lowest dosage kavain and inconsistently altered by 400 and 600 mg while a decrease occurred after 30 mg clobazam. The beta centroid generally slowed down after both compounds. Thus, kavain seems to exert in the 200 mg dosage an initial vigilance-promoting effect while the same dosage at later times and the higher doses 400 and 600 mg are sedative.

Our pharmaco-EEG mapping results are in agreement with the visually evaluated vigilosomnograms of Amman (1979), who described in 18 healthy volunteers also sedation after one week administration of 2×200 mg kavain. The pharmaco-EEG maps of the reference compound 30 mg clobazam are of the same type as described by other

investigators after benzodiazepines (Itil *et al.*, 1985; Saletu *et al.*, 1987, 1988, 1989; Hermann and Schärer, 1986, Buchsbaum *et al.*, 1985). Moreover, our present multi-lead pharmaco-EEG results are in agreement with our own previous single-lead findings (Saletu *et al.*, 1985).

Time-efficacy calculations demonstrated after kavain a first pharmacodynamic peak in the 1st to 2nd hour, and a 2nd one in the 8th hour while 30 mg clobazam showed two peaks in the 1st and 6th hour. These neuro-physiological findings indicate that both compounds have active metabolites (dehydrokavain which itself is one of the 5 main kava-pyrones of the kava plant root as well as n-desmethyl clobazam, respectively.) The pharmacodynamic peak of kavain coincides with the pharmaco-kinetic one, as the drug is rapidly absorbed showing peak plasma levels at 1·8 hours after 200 mg, distribution phase of 3–5 hours ($t\ ½\ \alpha$: 50 minutes) and an elimination half life of 9 hours (t ½ ß: 9 hours). The plasma level of the main metabolite para-hydroxykavain peaks also 1·7 hours post oral drug administration but has a longer elimination half life of 29 hours.

Kavain differs from the 1,5 - benzodiazepine clobazam not only in regard to type, extent and time - course of CNS changes but regarding the topographic aspects of the latter. Mapping the location of the most pronounced changes over time as well as the differences between the 3 kavain dosages placebo, and the reference compound, we observed generally the maximum of kavain effects over the frontal areas (with a right-sided accentuation) while the maximum of the clobazam-induced alterations lay over the central and parietal regions.

Psychometric investigations demonstrated marked differences between the two compounds also at the behavioural level. While kavain produced an improvement in the noopsyche as compared with placebo, opposite findings were observed after 30 mg clobazam in these young volunteers. Specifically, we noted after kavain in all 3 doses an improvement of intellectual performance (Pauli test), attention, concentration and reaction time, while 30 mg clobazam deteriorated performance in the Pauli test and reaction time task, and decreased attention, psychomotor activity and numerical memory. Our data are in agreement with earlier clinical observations and psychometric findings of Kretschmer (1970, 1975), Krueger and Kell (1977), and Ambrozi (1979). The clobazam data are also in agreement with our earlier findings (Saletu *et al.*, 1985) as we described after 30 mg clobazam a decrease in attention of healthy young volunteers while 20 mg of the compound did not influence significantly any noopsychic variable.

The thymopsyche was also differentially influenced by the 2 compounds but also by different kavain-doses. While there was an improvement after the lowest dosage of kavain, higher doses and the reference compound produced changes in the opposite direction which suggests sedation. Indeed, anxiolytic-sedative effects of kavain have been described by Kretschmer (1970, 1974), Kryspin-Exner (1974), Krueger and Kell (1977), Ammann (1979) and Krach (1986), as well as by Hunt *et al.* (1974). Coste-Simonin and Krantz (1975), Cottin *et al.* (1975), Martin (1975) after clobazam. Concerning our own studies about the action of 30 mg clobazam on mental and psychomotor performance as well as on thymopsychic variables it is of interest that we found this time more sedation that in our first study. However, as Hindmarch (1979) pointed out, the effect of anxiolytic sedatives on performance depends very much on the baseline which he described in a U-shaped fashion. While subjects with high anxiety demonstrated poor performance, they improved when anxiety was reduced. Normal subjects, on the other hand, receiving anxiety-reducing drugs may be expected to show a performance impairment because they would move to the lower (impairment) part of the bell-shaped curve (Malpas *et al.*, 1974). An interesting aspect of our computer-assisted measurements of motor speed in the rigidity test seems to be the fact that after kavain speed improved much more in the left than right hand which in turn may be associated with the location of the maximal drug-induced changes in the EEG topograms - namely over the right frontal areas.

Finally, our psychophysiological investigations demonstrated that there were only minimal alterations after both compounds. As is known, tranquilizers induce only little autonomous nervous system reactions. There were neither clinically nor statistically significant changes in pulse rate and blood pressure. Evaluation of somatic findings and side effects suggested that both compounds but particularly kavain were well tolerated.

ACKNOWLEDGEMENTS

The authors would like to express their thanks to Drs. Utikal and Steffens of Klinge Pharma, FRG

for supplying the drugs; to Mrs. Eva Kotai, medical illustrator, to Mr. Helmut Bernhardt, photographer; to Ms. Linda de los Santos, secretary; and to the entire staff of the Section of Pharmacopsychiatry of the Psychiatric University Clinic of Vienna for their valuable assistance in this project.

REFERENCES

Ambrozi, L. (1979). Der Einfluß von D, L-Kavain (Neuronika R) auf Konzentrationsfähigkeit, Kurzzeitgedächtnis, Reaktionssicherheit und Reaktionsgeschwindigkeit. *Therapiewoche*, **29**, 5967–5970.

Ammann, M. (1979). *Zerebrale Funktionsänderungen nach Kavain*. Inagural-Dissertation. Ludwig Maximilians Universität, München.

Anderer, P., Saletu, B., Kinsperger, K. and Semlitsch H. (1987). Topographic brain mapping of EEG in neuropsychopharmacology. Part I. Methodological aspects. *Methods and Findings in Experimental and Clinical Pharmacology*, **9**, 371–384.

Bartels, P. H. and Subach, J. A. (1976). Automated interpretation of complex scenes. In *Digital Processing of Biomedical Imagery*, Preston, E., Onoe, M. (Eds), Academic Press, New York, pp. 101–114.

Buchsbaum, M. S., Hazlett, E., Sicotte, N. Stein, M., Wu, J. and Zetin, M. (1985). Topographic EEG changes with benzodiazepine administration in generalized anxiety disorder. *Biological Psychiatry*, **20**, 832–842.

Coste-Simonin, A. and Krantz, D. (1975). Etude clinique d'une nouvel anxiolytique en cardiologie: le clobazam. *Gazette Med. de France*, **82**, 4460–4464.

Cottin, M., Dachary, J. M., Marie, C., Pagott, R., Ramant, J. and Salex, M. (1975). Etude d'un nouvel anxiolytique, le clobazam, dans l'anxiété résiduelle des psychotiques. *J. Pharmac. Clin.*, **2**, 81–87.

Duffy, F. H., Bartels, P. H., and Burchfiel, J. L. (1981). Significance probability mapping: An aid in the topographic analysis of brain electrical activity. *Electroencephalography and Clinical Neurophysiology*, **51**, 455–462.

Gasser, T., Bächer, P., and Möcks, J. (1982). Transformations towards the normal distribution of broad band spectral parameters in the EEG. *Electroencephalography and Clinical Neurophysiology*, **53**: 119–124.

Grünberger, J. (1977). Psychodiagnostik des Alkoholkranken. *Methodischer Beitrag zur Bestimmung der Organizität in der Psychiatrie*. Wien: Maudrich.

Grünberger, J., Linzmayer, L. und Saletu, B. (1984). Klinische Psychodiagnostik mit Hilfe psychophysiologischer Verfahren. *Wiener Medizinische Wochenschrift*, **134**, 29–35.

Grünberger, J., Linzmayer, L., Stöhr, H., Wittek, R. and Saletu, B. (1988). Computerunterstützte Rigiditätsmessung zur Differenzierung psychopathologischer Gruppen. *Wiener Medizinische Wochenschrift*, **9**, 206.

Herrmann, W. M. and Schärer, E. (1986). Das Pharmako-EEG und seine Bedeutung für die klinische Pharmakologie. In *Klinische Pharmakologie*, 4. Auflage, Kuemerle D. S., Hinterhuber, G. Spitzy, K. U. (Eds). Landberg: München, 1–71.

Hindmarch, I. (1979). Some aspects of the effects of clobazam on human psychomotor performance. *British Journal of Clinical Pharmacology*, **7**, 77S–82S.

Hunt, B. J., George, A. J. and Ridges, A. P. (1974). Preliminary studies in humans on clobazam (HR 376) – a new anti-anxiety agent. *British Journal of Clinical Pharmacology*, **1**, 174–175.

Itil, T. M., Shapiro, J. M., Eralp, E. Akman, A., Itil, K. Z. and Garbizu, C. (1985). A new brain function diagnostic unit, including the dynamic brain mapping of computer analyzed EEG, evoked potential and sleep (a new hardware/software system and its application in psychiatry and psychopharmacology). *New Trends in Experimental Clinical Psychiatry*, **1**, 107–177.

Krach, H. (1986). Wirksamkeit und Verträglichkeit des Naturstoffs Kavain als Psychopharmakon. Doppelblind-Prüfung von Neuronika R gegen Placebo. *Zeitschrift für Allgemeinmedizin*, **62**, 1028–1031.

Kretschmer, W. (1970). Kavain als Psychopharmakon. *Münchner Medizinische Wochenschrift*, **112**, (4), 154–158.

Kretschmer, W. (1974). Psychische Wirkungen von Kavain. *Münchner Medizinische Wochenschrift*, **116**, (14), 741–742.

Krueger, H. and Kell, G. (1977). Die Wirkung von Neuronika R auf die motorische Reaktionszeit und die visuell-mentale Verarbeitungszeit. *Therapiewoche*, **27**, 9417–9420.

Kryspin-Exner, K. (1974). Wirkung von Kavain bei Alkoholkranken in der Entziehungsphase. *Münchner Medizinische Wochenschrift*, **116** (36) 1557–1569.

Malpas, A., Legg, N. J. and Scott, D. F. (1974). Effects of hypnotics on anxious patients. *British Journal of Psychiatry*, **124**, 482–484.

Martin, J. C. (1975). Essai controlé d'un nouveau tranquillisant (le clobazam) chez des alcooliques chroniques en phase de sevrage. *J. Pharmac. Clin.*, **1**, 21–27.

Osgood, C. D., Suci, G. J., Suci, G. J. and Tannenbaum, P. H. (1975). *The Measurement of Meaning*. Urbana University Press.

Saletu, B., Grünberger, J., Berner, P. and Koeppen, D.: One difference between 1,5-and 1·4 benzodiazepines: Pharmaco-EEG and psychometric studies with clobazam and lorazepam. In *Clobazam. Human Psychopharmacology and Clinical Applications*, Hindmarch, I., Stonier, P. D., Trimble, M. R. (Eds) International Congress and Symposium Series, No. 71. Royal Society of Medicine, London, pp. 23–46.

Saletu, B., Anderer, P., Kinsperger, K. and Grünberger, J. (1987). Topographic brain mapping of EEG in neuropsychopharmaocology. Part II. Clinical applications (Pharmaco-EEG imaging). *Methods and Findings in Expermental and Clinical Pharmacology*, **9** (6) 385–408.

Saletu, B., Grünberger, J., Anderer, P. and Barbanjo, M. J. (1988). Pharmacodynamic studies of a combination of lorazepam and diphenhydramine and its single components: Electroencephalographic brain mapping and safety evaluation. *Current Therapeutic Research*, **44** 5, 907–937.

Saletu, BN., Anderer, P., Kinsperger, K., Grünberger, J. and Sieghart, W. (1989). Comparative bioavailability studies with a new mixed-micelles solution of diazepam utilizing radioreceptor assay, psychometry and EEG brain mapping. *International Clinical Psychopharmacology*.

Zerssen, V. D., Koeller, D. M. and Rey, E. R. (1970). Die Befindlichkeitssakala (B–S) – ein einfaches Instrument zur Objektivierung von Befindlichkeitsstörungen, insbesondere im Rahmen von Längsschnittuntersuchungen. *Arzneimittel-Forschung Drug Research*, **20**, 915–918.